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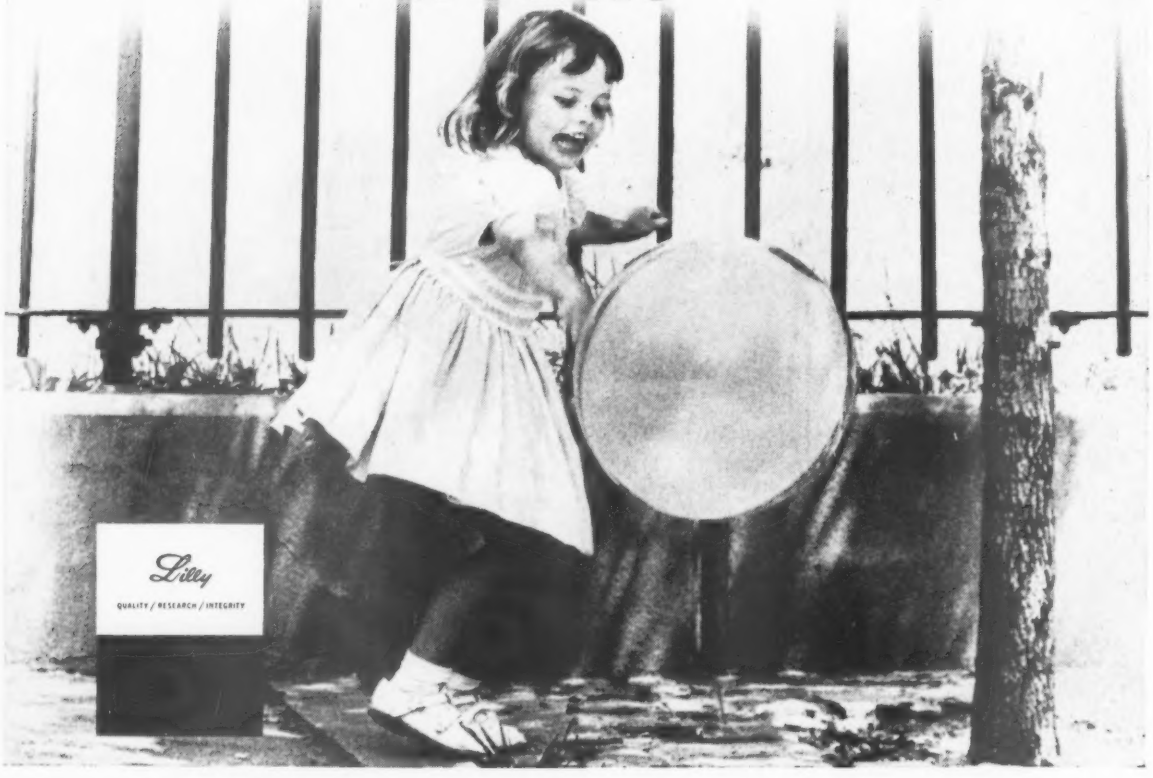

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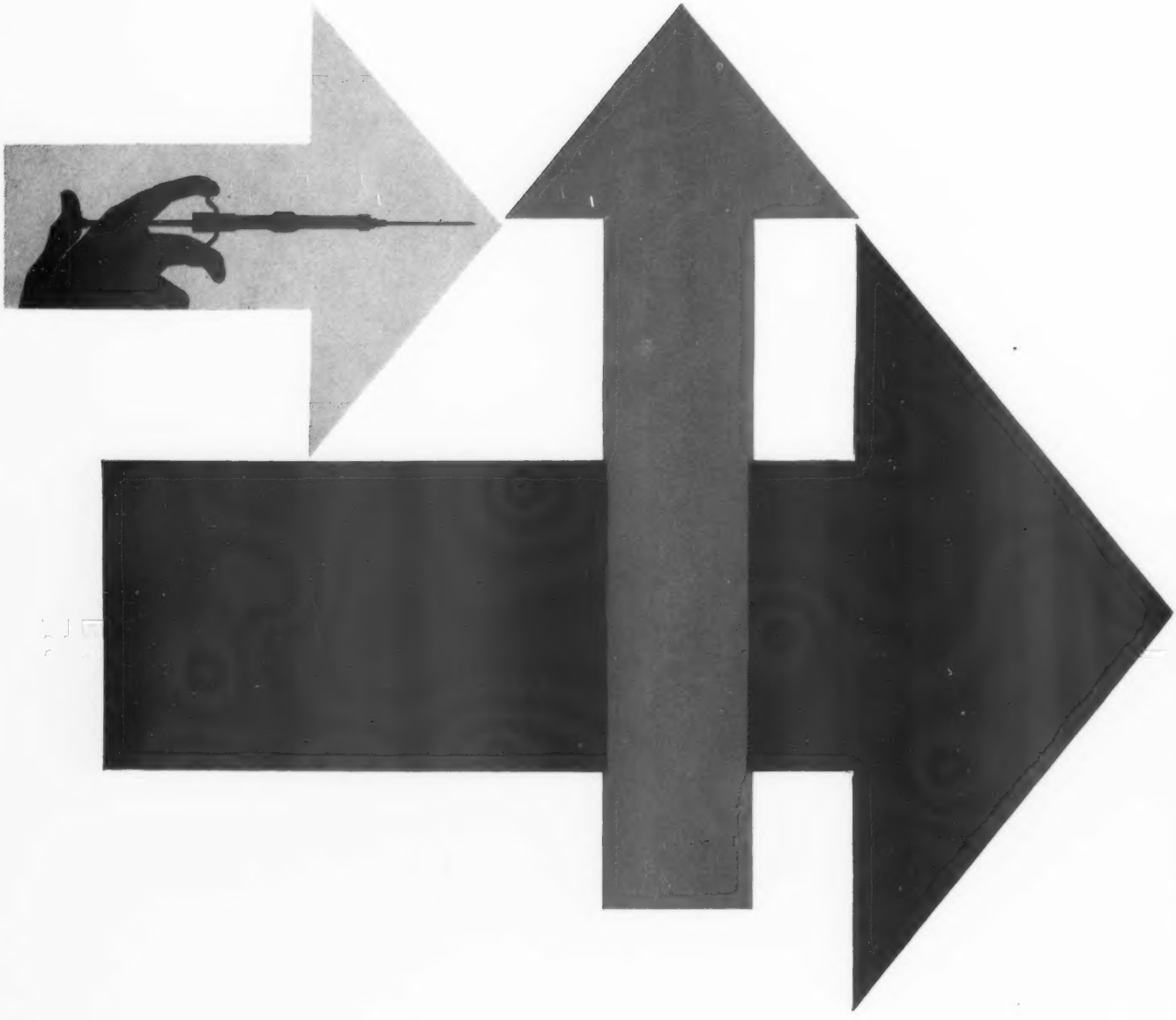

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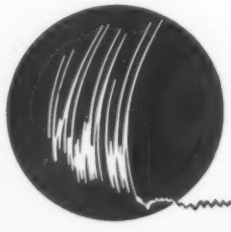
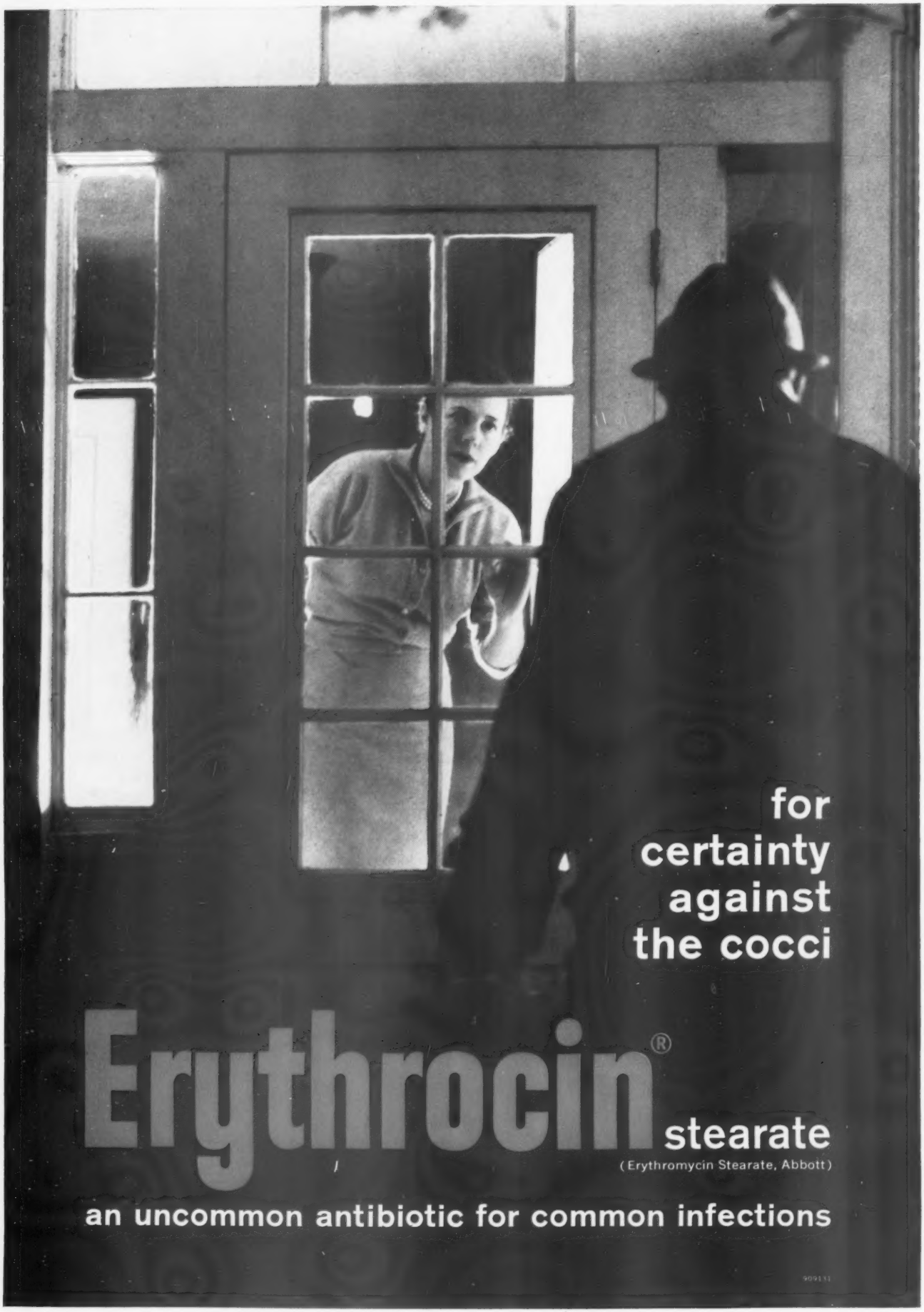


in vivo measurement of LUTREXIN on contracting uterine muscle

HYNSON, WESTCOTT & DUNNING, INC. H&WD BALTIMORE 1, MARYLAND


for
certainty
against
the cocci
Erythrocin®
stearate
(Erythromycin Stearate, Abbott)
an uncommon antibiotic for common infections

AFTER MILLIONS OF PRESCRIPTIONS

...AN UNPARALLELED SAFETY RECORD

provides fast, high blood and tissue concentrations

Because ERYTHROCIN Stearate is rapidly absorbed, patients get therapeutic blood and tissue levels within 30 minutes. High peak levels occur between one and two hours—and effective concentrations are maintained for at least six hours.

backed by years of clinical effectiveness

Actually, every prescription for ERYTHROCIN is backed by years of clinical efficacy against coccal infections. And, with the problem of antibiotic resistance becoming more important daily, the value of ERYTHROCIN as a day-to-day anticoccal agent is dramatically underlined.

supported by an unparalleled safety record

During all the years ERYTHROCIN has been prescribed, serious reactions have been practically nonexistent. Unlike penicillin, allergy is no problem. And, in contrast to "broad-spectrum" action, the normal flora of the intestinal tract is virtually unaltered with ERYTHROCIN therapy.

offers bactericidal activity

Unlike broad-spectrum antibiotics, ERYTHROCIN is classed as a bactericidal agent. It offers lethal action against coccal invaders—resulting in prompt clinical response.

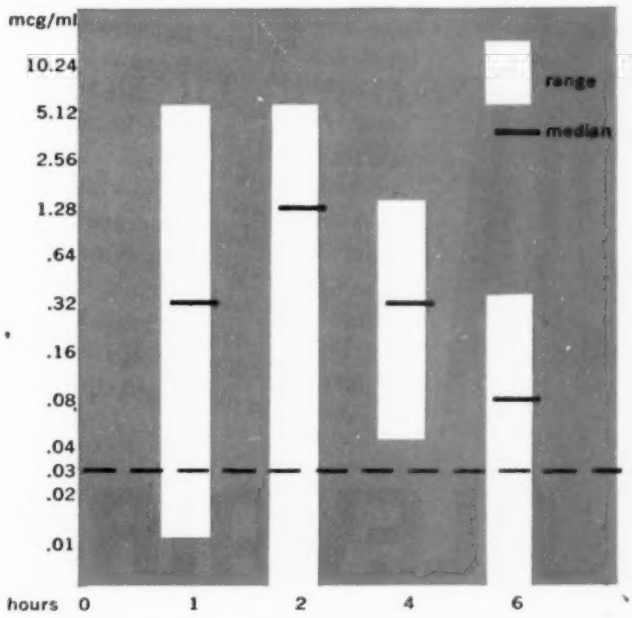
provides convenient dosage forms

Usual adult dose is 250 mg. four times daily. Children's dosage is reduced in proportion to body weight.

ERYTHROCIN comes in Filmtabs® (100 and 250 mg.), bottles of 25 and 100. Also, in a tasty, citrus-flavored oral suspension.

if you're concerned with blood levels . . .

Dotted line shows actual inhibitory concentrations against most organisms. Note the high ranges and medians of ERYTHROCIN Stearate at one, two, four and six hours. Data represents three studies with adults. Each was given one 250-mg. Filmtab.



And where you need a consistent uniform response that only an injectable form can provide, remember—**ERYTHROCIN-I.M.** (Erythromycin Ethyl Succinate, Abbott) and **ERYTHROCIN LACTOBIONATE.**

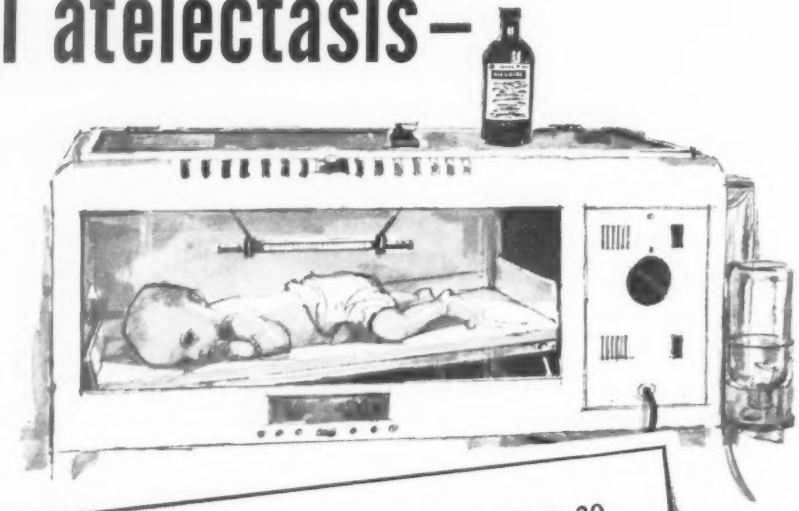
®Filmtab—Film-sealed tablets, Abbott; U.S. Pat. No. 2881085

ABBOTT

ALEVAIRE® aerosol in the hospital

in neonatal atelectasis–

*". . . results are impressive. This dreaded condition usually improved in a few hours, and it was really striking to see a cyanotic baby with gasping respirations and suprasternal retraction become relaxed and pink in such a short period of time."**



CASE REPORT

A typical Alevaire case history—D., a premature male infant (28 to 30 weeks) was delivered as a frank breech. Weight was 3 lb., 6 oz. After birth the patient's condition was poor; shallow, irregular respiration, suprasternal retraction, gasping and cyanosis were present. Breath sounds were diminished, and bilateral atelectatic rales were observed.

The infant was placed in an optimal oxygen concentration in an incubator. Although color and respiration somewhat improved, he remained lethargic. His condition became worse the following day, and respirations were rapid and shallow.

Alevaire aerosol was started and antibiotics were given. Within three hours respiration was deeper and easier, the color improved, and the infant was crying vigorously. Nine hours later, after continued improvement, the lungs were better aerated, the color was pink and respiration was regular.

The next day, the lungs were almost clear on auscultation and no respiratory distress was noted. Therapy was discontinued on the third day; the patient was discharged six weeks later weighing 5 lb., 7 oz.

Alevaire is supplied in bottles of 60 cc. for intermittent therapy and in bottles of 500 cc. for continuous inhalation therapy.

ALEVAIRE

Winthrop LABORATORIES
NEW YORK 18, N. Y.

has been dramatically effective in:

- neonatal asphyxia (due to inhalation of amniotic fluid, mucus obstruction, atelectasis)
- croup • laryngitis • tracheobronchitis
- pertussis • pneumonia • bronchial asthma
- emphysema • bronchiectasis • lung abscess
- pneumoconiosis • smoke, kerosene poisoning
- poliomyelitis (respiratory complications)
- routine oxygen therapy • tracheotomy
- prevention of postoperative pulmonary complications

*Smessaert, Andre; Collins, V. J.; and Kracum, V. D.: *New York Jour. Med.*, 55:1587, June 1, 1955.

Alevaire, trademark reg. U.S. Pat. Off.

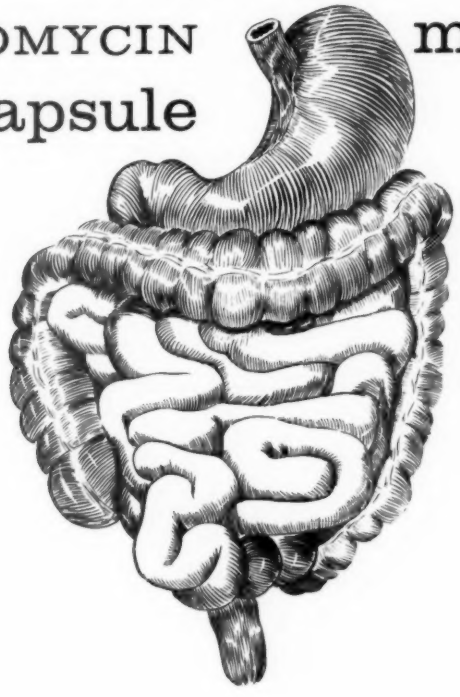
DECLOMYCIN NOTES:

Demethylchlortetracycline Lederle

antibiotic

toleration

reduction in incidence and/or severity of gastrointestinal side effects may be attributed to the far lower DECLOMYCIN milligram intake (per capsule and per day)[1-3]



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Capsules, 150 mg.—Pediatric Drops, 60 mg./cc.—Oral Suspension, 75 mg./5 cc. tsp.

GREATER ACTIVITY... FAR LESS ANTIBIOTIC... UNRELENTING-PEAK CONTROL..."EXTRA-DAY" PROTECTION AGAINST RELAPSE

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

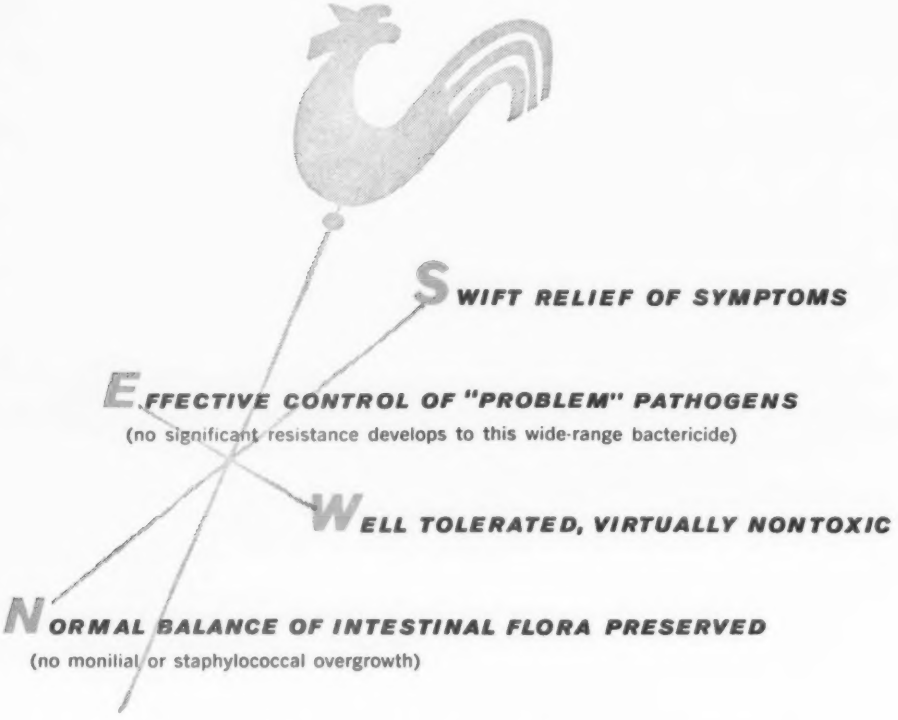
TO STOP DIARRHEA

from all points... growing evidence favors

FUROXONE®

brand of furazolidone

▪ Pleasant-flavored LIQUID, 50 mg. per 15 cc. (with kaolin and pectin) ▪ Convenient TABLETS, 100 mg. ▪ Dosage—400 mg. daily for adults, 5 mg./Kg. daily for children (in 4 divided doses).

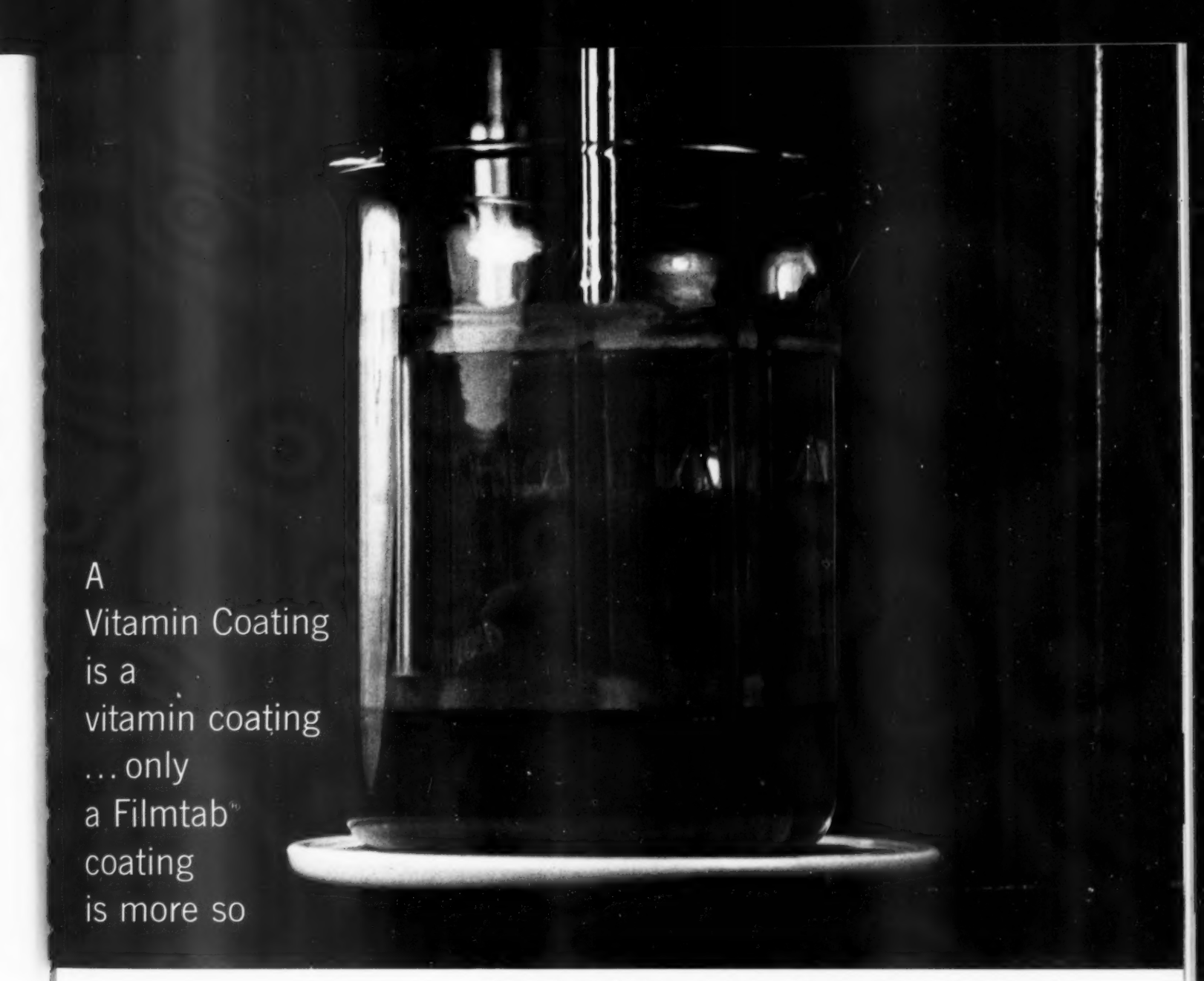


From a Large Midwestern University: FUROXONE Controls Antibiotic-Resistant Outbreak. An outbreak of bacillary dysentery due to Shigella sonnei was successfully controlled with FUROXONE after a broad-spectrum antibiotic had proved inadequate. Cure rates (verified by stool culture) were 87% with FUROXONE, 36% with chloramphenicol. Only FUROXONE "failures" were those lost to follow-up. Chloramphenicol failures subsequently treated with FUROXONE responded without exception. FUROXONE was also used effectively as prophylaxis and to eliminate the carrier state. It was "extremely well tolerated in all 191 individuals who received it either prophylactically or therapeutically."

Galeota, W. R., and Moranville., B. A.: Student Medicine (in press)

THE NITROFURANS—A UNIQUE CLASS OF ANTIMICROBIALS

EATON LABORATORIES, NORWICH, NEW YORK



A Vitamin Coating is a vitamin coating ... only a Filmtab® coating is more so

Above: Filmtab Optilets, seconds after being immersed in a test beaker of gastric and intestinal fluids. Note that disintegration has already started.

IT WILL STAND UP ALONGSIDE THE TOUGHEST SUGAR COATING MADE.
YET, IT CUTS BULK UP TO 30%.

IT ACTUALLY RESISTS DETERIORATION BETTER THAN MOST SUGAR COATINGS.
YET, IT WILL DISSOLVE FASTER IN THE STOMACH.

IT'S SO THIN IT PRACTICALLY BECOMES THE TABLET ITSELF.
YET, IT SEALS IN ALL VITAMIN ODORS AND TASTE.

It's not too hard to engineer a tablet coating that will stand up against a battery of control tests. The trick is to make it so that it will still dissolve on schedule in the body.

That's one of the unusual things about Filmtab, Abbott's anhydrous film coating process. The Filmtab coating is micro-thin—but it will take all the tests for durability and climate as well as, or better than, most sugar coatings. Yet, it will dissolve almost immediately in the body. It won't chip or break. It seals in odors. It cuts the size of the tablet.

Is all this so important? Well, the formula is the big thing, of course. But the little things sometimes are the nice things. They make vitamin-taking that much pleasanter. And you don't pay a penny extra for them . . . with "Vitamins by Abbott."

ABBOTT

You can get a full line of "Vitamins by Abbott" in Table Bottles... at no extra cost

[filmtab] **DAYALETS®** TABLE BOTTLE (100'S); BOTTLES OF 50 & 250
[filmtab] **DAYALETS-M®** APOTHECARY BOTTLES 100 & 250

Two extra-potent maintenance formulas; ideal for those who are "run-down" nutritionally, or as prophylaxis for those on a restricted diet.

each Filmtab **DAYALETS** represents:

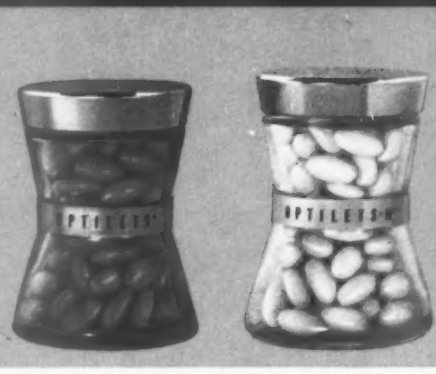
Vitamin A	3 mg. (10,000 units)
Vitamin D	25 mcg. (1000 units)
Thiamine Mononitrate	5 mg.
Riboflavin	5 mg.
Nicotinamide	25 mg.
Pyridoxine Hydrochloride	2 mg.
Vitamin B_{12} (as cobalamin concentrate)	2 mcg.
Folic Acid	0.25 mg.
Calcium Pantothenate	5 mg.
Ascorbic Acid	100 mg.

Dosage: Just one Filmtab daily for prophylaxis; two or more daily for therapeutic effect.

each **DAYALETS-M** represents all of Dayalets' vitamins, plus the following:

Iron (as sulfate)	10 mg.
Copper (as sulfate)	1 mg.
Iodine (as calcium iodate)	0.15 mg.
Cobalt (as sulfate)	0.1 mg.
Manganese (as sulfate)	1 mg.
Magnesium (as oxide)	5 mg.
Potassium (as sulfate)	5 mg.
Zinc (as sulfate)	1.5 mg.
Molybdenum (as sodium molybdate)	0.2 mg.

Dosage: One Filmtab daily, or as directed by physician.



[filmtab] **OPTILETS®**
[filmtab] **OPTILETS-M®**
TABLE BOTTLES OF 30 & 100.
BOTTLES OF 1000.

Therapeutic formulas for the more severe deficiencies—excellent for use when bodily requirements are increased, as in periods of illness or infection.

each **OPTILETS** Filmtab represents:

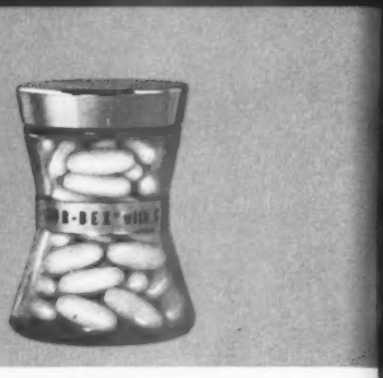
Vitamin A	7.5 mg. (25,000 units)
Vitamin D	25 mcg. (1000 units)
Thiamine Hydrochloride	10 mg.
Riboflavin	5 mg.
Nicotinamide	100 mg.
Pyridoxine Hydrochloride	5 mg.
Folic Acid	0.3 mg.
Vitamin B_{12} (as cobalamin concentrate)	6 mcg.
Calcium Pantothenate	20 mg.
Ascorbic Acid	200 mg.

Dosage: One or two Filmtabs daily, or as directed by the physician.

each **OPTILETS-M** represents all the vitamins of Optilets, plus the following:

Iron (as sulfate)	10 mg.
Copper (as sulfate)	1 mg.
Iodone (as calcium iodate)	0.15 mg.
Cobalt (as sulfate)	0.1 mg.
Manganese (as sulfate)	1 mg.
Magnesium (as oxide)	5 mg.
Potassium (as sulfate)	5 mg.
Zinc (as sulfate)	1.5 mg.
Molybdenum (as sodium molybdate)	0.2 mg.

Dosage: One or two Filmtabs daily, as directed by physician.



[filmtab] **SUR-BEX® with C**
TABLE BOTTLE OF 60.
BOTTLES OF
100, 500 & 1000

The therapeutic B-complex formula with vitamin C: . . especially useful after illness or in pre- and post-surgical situations.

each **SUR-BEX WITH C** Filmtab represents:

Thiamine Mononitrate	6 mg.
Riboflavin	6 mg.
Nicotinamide	30 mg.
Pyridoxine Hydrochloride	1 mg.
Vitamin B_{12} (as cobalamin concentrate)	2 mcg.
Calcium Pantothenate	10 mg.
Ascorbic Acid	150 mg.
Desiccated Liver, N.F.	300 mg.
Brewer's Yeast, Dried	150 mg.

Dosage: As a dietary supplement, 1 or 2 Filmtabs daily; in convalescence, 2 or more Filmtabs daily.

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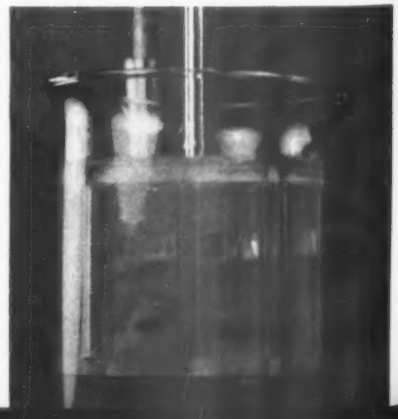

toward a new beginning...

meaningful "give and take" experience
within the hospital community

for a psychiatric case report with a happy ending, turn the page...

toward the "give and take" recovery goal

1 Turmoil, fear and frozen behavior in a paranoid patient are mixed reactions to social situations. TRILAFON, I.M., started.

Beginning of responsiveness, trust in therapist. Suspicion diminished, responsiveness improving. 2

4 Consistently considerate treatment from hospital personnel supports the emerging sense of values and purpose.

3 A clear turning point, and a quiet clear frame of mind. TRILAFON continued orally, 12 mg. q.i.d.

5 Six months later, staff notes a major "profile" change as the patient "holds his own" successfully in the daily interrelationships of the hospital community.

facilitates social improvement... the initial goal of therapy in mental patients

Trilafon®

perphenazine

Dosage: Depending on the severity of the condition and response of the individual case, the dosage is 8 to 16 mg. two to four times daily. Consult Schering literature for other indications, as well as for details on dosage and administration, precautions and contraindications.

Packaging: Tablets—2 mg., 4 mg. and 8 mg., bottles of 50 and 500; 16 mg., bottle of 500. REPETABS—4 mg. in the outer layer and 4 mg. in the timed-action inner core, bottles of 30 and 100. TRILAFON Injection—5 mg., ampul of 1 cc., boxes of 6 and 100; 10 cc. vial, 5 mg./cc., boxes of 1 and 10. TRILAFON Concentrate—16 mg./5 cc., bottle of 4 oz., with graduated dropper. TRILAFON Suppositories—4 mg. and 8 mg., boxes of 6. TRILAFON Syrup—2 mg./5 cc., 4 oz. bottle.

TRILAFON,® brand of perphenazine.
REPETABS,® Repeat Action Tablets.

Schering

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8-334

SPONTIN®

(Ristocetin, Abbott)

A STATISTICAL REVIEW* OF THREE HUNDRED THIRTY-THREE CASES

**Records of Medical Department, Abbott Laboratories, North Chicago, Illinois*

SPONTIN (Ristocetin, Abbott) is a new antibiotic discovered and developed at Abbott Laboratories. Its two components, and B, have been isola line state from the fer of a new species of *Nocardia lurida*. Bot are active against gra teria and mycobacter mycete was isolated f ple collected from th Gods, Colorado Sp No other culture wh same antibiotic has

The chemical cha ristocetins are not c though they are kn teric substances con phenolic groups a ristocetin A and ris molecules with m the vicinity of 4000 have good stability pH range of bloo SPONTIN is a ly tion, derived fr material, represe ristocetins A an

Antimicrobial tion against gra ganisms, SPONT effective than able antibiotics

Against pne cocci (except s cocci) the anti tericidal at th concentration hibits the gro also kills the

This obse for the majo lococci. Ho staphylococ have been t centration s minimum i produce a this reason SPONTIN i for the trea and enterococcal infections.

Cultures of staphylococcus aureus, which are resistant to other antibiotics have been shown to be sensitive to SPONTIN. There has been no case reported in which a staphylococcal or enterococcal strain has exhibited a

SPONTIN

pH range of blood a

SPONTIN is a lyophilized preparation, derived from pure crystalline material, representing a mixture of ristocetins A and B.

Antimicrobial Properties. In its action against gram-positive coccal or- isms, SPONTIN is notably more ntly avail-

d strepto- of entero- riably bac- sage. The which in- organisms

holds true s of staphy- strains of cocci which uired a con- gher than the ncentration to effect. It is for her dosage of recommended staphylococcal tions.

coccus aureus, other antibi- to be sensitive s been no case aphylococcal or has exhibited a SPONTIN.

that the antibi- TIN is enhanced gamma globulin. supported by the *vivo* activity of mes greater than from the *in vitro*

estigators* have re- cal response follow- ration of SPONTIN dies have shown a ity on the part of ganism. Satisfactory may be expected sm requires up to 25 ONTIN for inhibition llowing table shows nsitivities of different he major pathogenic

Summary and Conclusions

Major use has been treating staphylococcic infections. Of the total 333 cases, approximately one-third was treated for pneumonia; of these over 80% were either cured or improved. About 70% of these pneumonias were caused by staphylococci.

The next largest group included 46 patients with subacute bacterial endocarditis. About 50% of these infections were identified as staphylococcic and a further 15% as enterococcic. Other infections included 38 cases of septicemia, 32 abscesses and 24 patients with osteomyelitis.

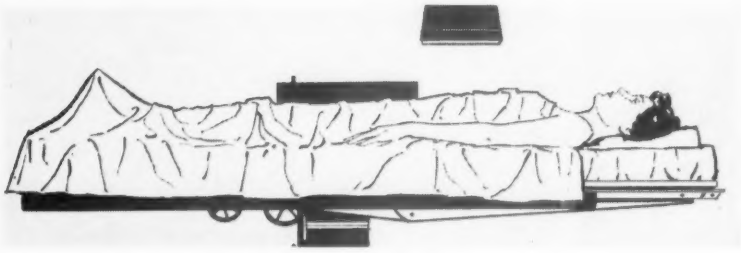
The administration of SPONTIN brought about a cure in 60% of all the cases reviewed and improvement in a further 17%.

Side-effects were seldom troublesome when a daily dose of 2 Gm. was not exceeded. The incidence rose as the dosage was increased. The most disturbing side-effect after administration of SPONTIN has been neutropenia. However, in all instances this has responded to either discontinuance of medication or reduction in dose.

909146

Better opacification and delineation of the gallbladder

ORABILEX more closely approaches the ideal degree of opacification than any other medium. Better density results in improved radiologic quality of the film and greater diagnostic accuracy without obscuring or concealing pathology.



A big plus is economy.
Better opacification and patient acceptance means fewer repeat examinations. The need for additional films because of obscuring intestinal shadows is also less with Orabilex. Satisfactory performance on the first try adds up to savings in the long run.

Greater patient acceptance

Diarrhea and dysuria are virtually non-existent, and other gastro-intestinal complaints are minimal. ORABILEX has this marked advantage over other contrast media.

ORABILEX*

Bunamiodyl

new cholecystographic medium

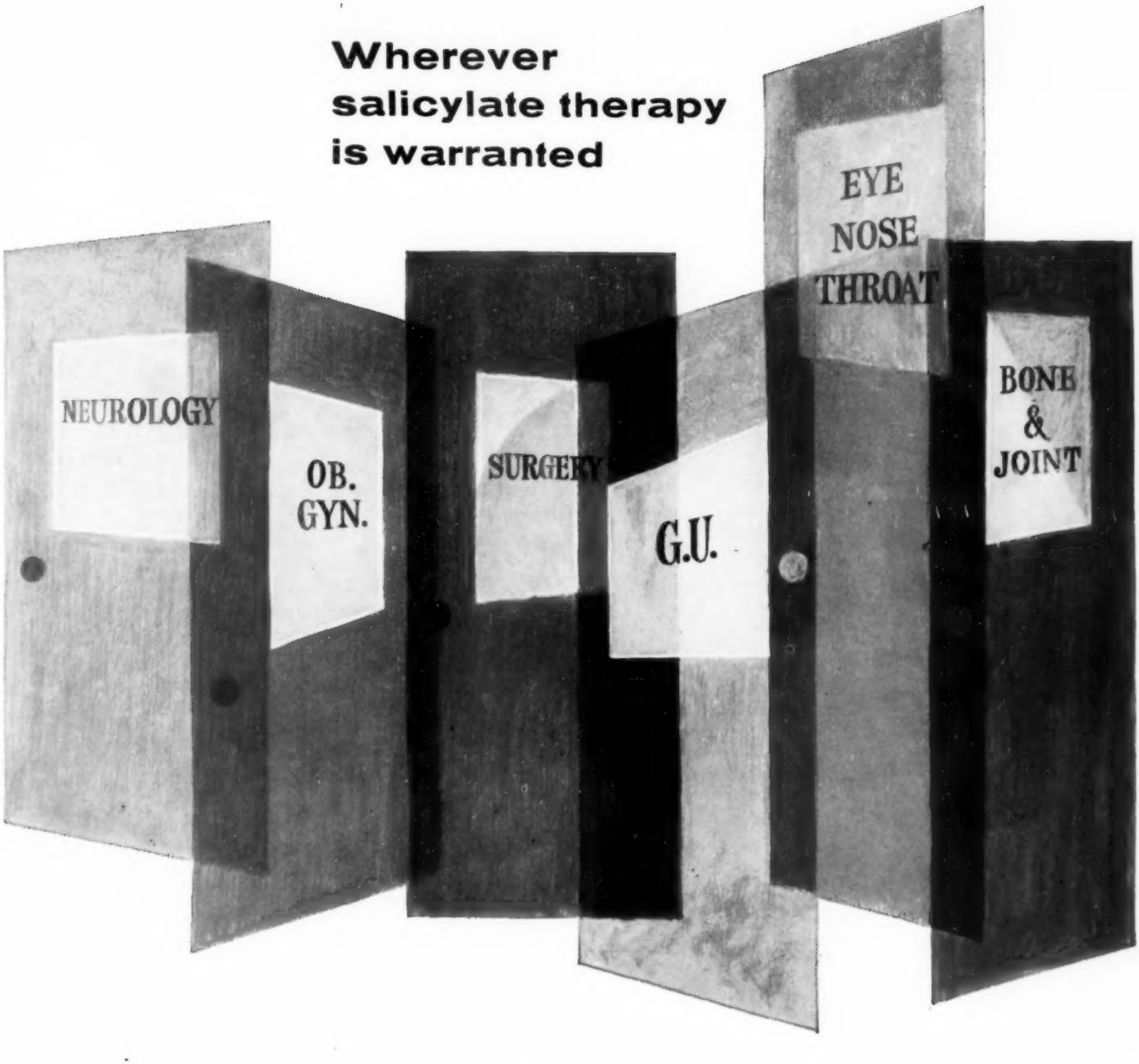
with superior "look-through" quality

*T.M. A development of Guerbet Laboratories

FOUGERA

E. FOUGERA & COMPANY, INC. Hicksville, Long Island, New York

Wherever salicylate therapy is warranted



BUFFERIN®

brings fast relief and avoids upset stomach

- reduces patients' complaints
- saves time for nurses and aides
- improves hospital efficiency and economy
- offers exclusive hospital size Bufferin 1000's

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A highly appreciated patient service

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A ROUTINE USE ITEM — at every bedside. Antibacterial Cēpacol helps cut down the passage of oral pathogens from patient to patient. As a mouthwash, Cēpacol overcomes unpleasant taste.

Up to 75% Profit — on each Cēpacol Bedside Bottle . . . *an exclusive plan for hospitals!*

Cēpacol

a pleasant taste that lasts!

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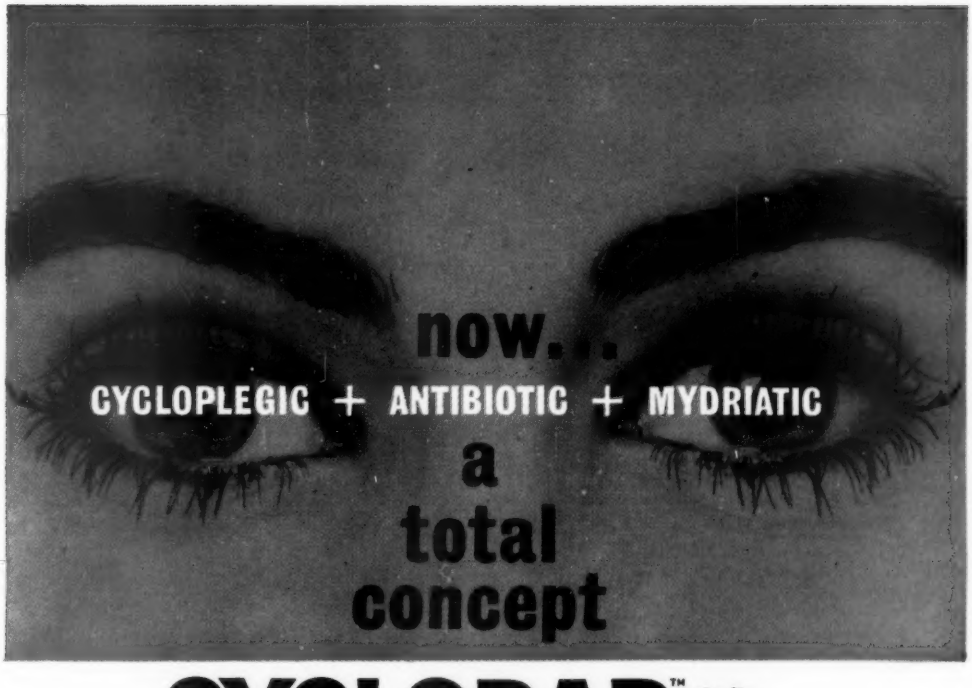

CYCLOBAR™ sterile ophthalmic gel

(CYCLOGYL® HCl 1.0% [cyclopentolate hydrochloride, Schieffelin], methylcellulose, and neomycin citrate 0.55%.)

Fast-acting cycloplegic and mydriatic agent[1] plus the potent antibiotic action of neomycin—"...effective against [a wide] range of organisms met in ocular infections...."[2] Unexcelled for pre- and post-operative therapy, infectious disorders and injured eyes. Holds the pupil in an open, relaxed position ...controls infection...helps prevent adhesions... relieves inflammation. Long-acting CYCLOBAR can't be blinked out. When desired, miotics will return the eye to normal within 6 hours;[3] without miotics, the eye will return to normal in 24 hours.[4] No evidence of irritation or sensitization has been reported.

References: 1. Miles, P. W.: Missouri Med. *56*:1243, 1959. 2. Sorsby, A.: Ann. Roy. Coll. Surgeons of England *22*:107, 1958. 3. Costner, A. N.: South. M. J. *48*:1192, 1955. 4. Rasgorshek, R. H., and McIntire, W. C.: Am. J. Ophth. *40*:34, 1955.

Supplied in collapsible tubes of 3.54 Gm.
Samples and literature available on request.

Schieffelin & Co. / Since 1794
PHARMACEUTICAL LABORATORIES DIVISION, New York 3, N. Y.

new CYCLOGYL® gel

Prompt, complete cycloplegia in new, long-acting gel form. Can't be blinked out, so its action is concentrated and prolonged. Can be used in conjunction with topical steroid or antibiotic therapy.

CYCLOGYL® FOR ALL-PURPOSE CYCLOPLEGIA

"...Acts so quickly and wears off so quickly that loss of time for doctor and patient is minimal."[1] Recovery within 6 hours or less with a miotic[2]...within 24 hours without.[3] Unexcelled for refraction...valuable for treatment of lesions, inflammatory conditions and pre- and postoperative therapy. No toxic or allergic reactions reported[4]...well-tolerated by children and elderly patients.[1,3]

CYCLOGYL® Gel
Sterile ophthalmic gel. (CYCLOGYL HCl 1.0% in a neutral gel, Schieffelin.)

CYCLOGYL®
Sterile ophthalmic solution. (cyclopentolate hydrochloride, Schieffelin.)

Supplied:
Dark-pigmented iris—2.0% solution with PVP (polyvinylpyrrolidone). 7.5 ml. and 2 ml. dropper bottles.
Brown or hazel iris — 1.0% solution. 15 ml. and 2 ml. dropper bottles.
Blue, gray and green iris—0.5% solution. 15 ml. dropper bottles.
Prolonged therapy — Gel. 3.54 Gm. collapsible tubes.
Samples and literature supplied on request.

References: 1. Miles, P. W.: Missouri Med. *56*:1243, 1959. 2. Costner, A. N.: South. M. J. *48*:1192, 1955. 3. Rasgorshek, R. H., and McIntire, W. C.: Am. J. Ophth. *40*:34, 1955. 4. Gordon, D. M., and Ehrenberg, M. H.: Am. J. Ophth. *38*:831, 1954.

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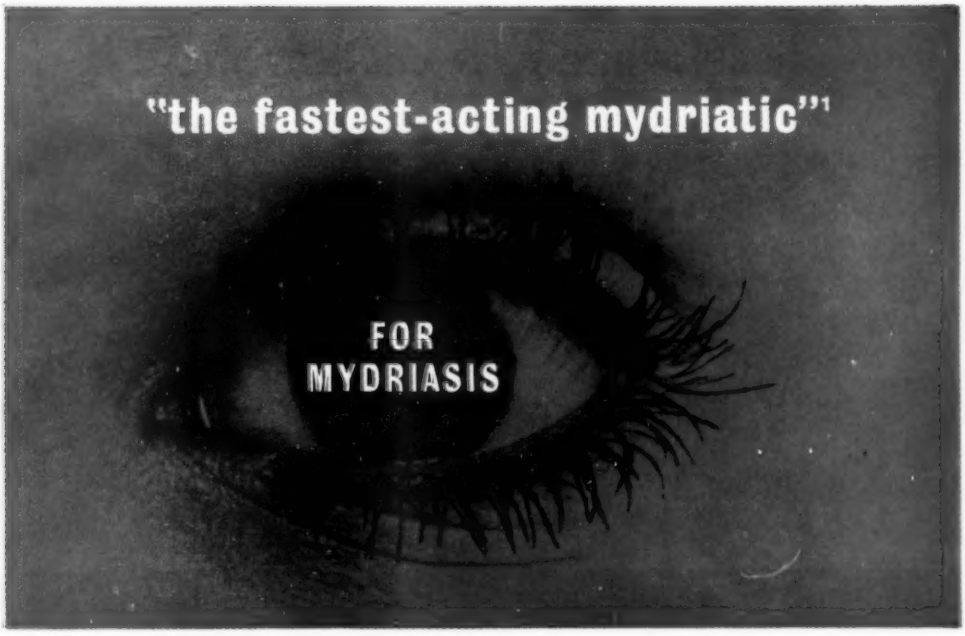

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References: 1. Miles, P. W.: Missouri Med. *56*:1243, 1959. 2. Priestly, B. S.; Medine, M. M., and Phillips, C. C.: to be published. 3. Costner, A. N.: South. M. J. *48*:1192, 1955. 4. Rasgorshek, R. H., and McIntire, W. C.: Am. J. Ophth. *40*:34, 1955. 5. New and Nonofficial Drugs: J. B. Lippincott Company, 1958, p. 243.

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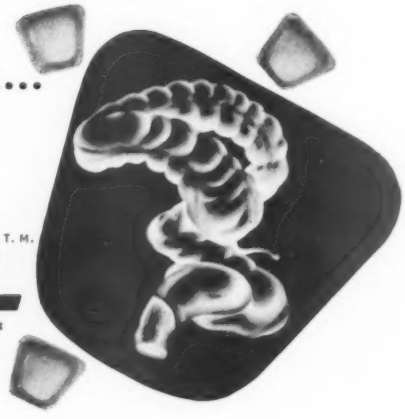

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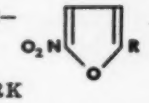

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Alabama Society

Mr. T. Earl Cobb assumed the duties of President of the Society of Alabama Hospital Pharmacists at the regular quarterly meeting in October. Mr. Cobb is associated with the Veterans Administration Hospital in Birmingham. Results of the elections included the following new officers: *Vice-President,* Clarence Gorman, Veterans Administration Hospital, Birmingham; *Secretary-Treasurer,* Mack Gamble, Carraway Methodist Hospital, Birmingham; and *President-Elect,* Harold Bishop, University Hospital, Birmingham.

In further action, the Society awarded an honorary membership, its first, to Mr. Elbert W. Gibbs, Secretary of the State Board of Pharmacy. It also took as a project for the coming year the development of a guide for control of drugs in small hospitals.

Northern California Society

For their November meeting, members of the Northern California Society of Hospital Pharmacists heard a description of a colony in the Hawaiian Islands where patients with Hanson's disease are treated. The meeting was held at the U.S. Public Health Service Hospital in San Francisco.

Mrs. Marie Kuck, a member of the Society, spoke on "Molokai—The Island of Christian Fortitude." Recently opened to visitors, Kalapapa, Molokai, now has 255 patients with Hanson's disease, compared to some 3,000 patients not many years ago. Mrs. Kuck described her plane trip to the island, a tour of the island's landmarks, and particularly the grounds of Kalapapa. A visit to the 65-bed hospital and its pharmacy was an interesting highlight. Mrs. Kuck also related the history of the early days of the colony and a picture of the social and economic life of the present inhabitants. Following the talk, slides taken during the trip were shown.

During the business meeting which followed, results of the recent elections were announced. The following officers will serve the Northern California Society during 1960: *President,* William Dudley; *Vice-President,* Charles Jackson; *Secretary,* George Gruber; and *Treasurer,* Ellen Berlin.

Colorado Society

The October meeting of the Colorado Society of Hospital Pharmacists was held at St. Joseph's Hospital in Denver.

A tape recording of a speech made by Joseph LaNier, President of the local Society, at the Colorado Pharmacal Association Convention in June was played. Mr. LaNier proclaimed that hospital pharmacy is not in competition with the drugstore, but is fully occupied with the care of those patients in the hospital. To illustrate this, he outlined the services the hospital pharmacy performs in its functions. Mr. LaNier further pointed out the joint responsibility of the retail and the hospital pharmacist—the responsibility to evaluate the standard of our profession.

The balance of the meeting was devoted to group discussion on problems faced by hospital pharmacies. Among those topics discussed were relationships with retail stores, education of hospital pharmacists, product information services, and the formulary system in the hospital.

Georgia Society

The Georgia Society of Hospital Pharmacists held its Second Annual Seminar on Hospital Pharmacy on October 31 and November 1. The Seminar was held at the Georgia Center for Continuing Education on the University of Georgia campus. Topics and speakers at the Seminar included the following:

Officers and Officers Elect of the Alabama Society of Hospital Pharmacists. Shown in photograph are (l. to r.) Clarence Gorman, Earl Cobb, Harold Bishop, Jack Cole, Millard Johnson, Ed Whiddon, Perry Cox, Mary Lancaster, Joe Vance, Mary Winters, and Sister Vincent Kurtzeman

"Hospital Pharmacy Trends," Mr. Grover C. Bowles, Director of Pharmacy Service, Baptist Memorial Hospital, Memphis, Tenn.

"The Newer Diuretics," a panel discussion led by Dr. John Stegeman, Medical Center, Athens, Ga.; Dr. Joseph P. La Rocca, School of Pharmacy, University of Georgia; and Dr. Douglas Johnson, Southern College of Pharmacy.

"Interprofessional Relationships in the Hospital," Mr. William E. Woods, Director of Hospital Relations, National Pharmaceutical Council, New York City.

"After-Hour Dispensing," Mr. Kenneth Flinchum, President of the South Carolina Society of Hospital Pharmacists and Chief Pharmacist at Self Memorial Hospital, Greenwood, S. C.

"Recruiting Program for Hospital Pharmacists," Mr. Allen A. Ford, President of the Florida Society of Hospital Pharmacists and Chief Pharmacist at Baptist Memorial Hospital, Jacksonville, Fla.

"Prepackaging Requirements and Samples," Mr. Charles E. Bruer, President of the Tennessee Society of Hospital Pharmacists and Chief Pharmacist at Jackson-Madison County General Hospital, Jackson, Tenn.

Illinois Society

The November meeting of the Illinois Society of Hospital Pharmacists was called to order by President Nelson Kitsuse at the Tinley Park State Hospital on Tuesday, November 10. Dr. John D. Cutler, Superintendent of the Hospital, welcomed members of the Society and briefly gave some of the facts and history about the Institution.

The meeting opened with a discussion of the possibility of the Society meeting once a year in some of the cities south of Chicago so that other hospital pharmacists in Illinois would have the opportunity to attend. Another suggestion made was that the Illinois Society sponsor another organization in Southern Illinois. A committee headed by Daniel Ravegnani will study the proposals and make recommendations at a later date.

Dr. William Gallagher, Chief of Therapeutics and Treatment at Tinley Park State Hospital, was the first speaker of the evening. Dr. Gallagher discussed the patients, methods of procedure, and present-day treatment of the mentally ill. He mentioned briefly the psychotherapeutic drugs and how they are used.

Mr. Robert H. Schmidt of Hoffmann-La Roche concluded the evening's program. Mr. Schmidt spoke on the monoamine oxidase inhibitors and their use as psychotherapeutic agents, the pharmacology, and the history behind their discovery and use.

Kansas City Society

Mr. W. F. Wilhelm of the Independence Sanatorium and Hospital, Independence, Missouri, was elected President of the Society of Hospital Pharmacists of Greater Kansas City at the November 10 meeting.

Other officers elected at this meeting were *Vice-President,* Sister Joseph Marie, St. Mary's Hospital, Kansas City, *Secretary,* Sister Eva Marie, St. Margaret's Hospital, Kansas City; and *Treasurer,* Hugh Prussing, St. Joseph Hospital, Kansas City.

Mr. J. C. Chipman reported that the Central Committee for Disaster Planning has accepted the list of drugs and biologicals submitted by his Committee to be made available to hospitals in case of general disaster.

Maryland Association

The Maryland Association of Hospital Pharmacists, in cooperation with Pfizer Laboratories and J. B. Roerig and Company, held a Hospital Pharmacy Seminar on November 24. The Seminar was held in the auditorium of the National Institutes of Health Clinical Center in Bethesda, Maryland.

Registrants were welcomed by Dr. Jack Masur, Assistant Surgeon General of the United States Public Health Service, and Director of the Clinical Center. In addition to Dr. Masur, members heard greetings from Mr. Paul Parker, Director of the Division of Hospital Pharmacy of the A.Ph.A., Mr. Burns Geiger of Pfizer Laboratories, and Mr. Milton Skolaut, Chief of the Pharmacy Department at the Clinical Center.

An interesting part of the all-day program was a closed-circuit television presentation of the pharmaceutical procedures in the pharmacy at the Clinical Center.

The well-balanced program presented the following speakers and their topics:

"Introduction of New Drugs," by Irvin Kerlan, M.D., Director of Research and Reference Branch, Bureau of Medicine, Food and Drug Administration.

"Planning of Emergency Equipment, Supplies and Medication for Dental Clinics in Hospitals," by Irwin Ship, D.D.S., Clinical Investigations Branch, National Institutes of Health.

"The Five-Year Pharmacy Course and Hospital Pharmacy," by Dean Noel E. Foss, School of Pharmacy, University of Maryland, Baltimore.

"Opportunities for Research in Hospital Pharmacy," by Mr. Robert Statler, Pharmacy Branch, Veterans Administration, Central Office, Washington, D.C.

"Established Principles, Standards and Resources," by Mr. Paul Parker, American Pharmaceutical Association, Washington, and Mr. Joseph Oddis, American Hospital Association, Chicago.

"New Drug Development," by Mr. Charles Rabe of J. B. Roerig and Company, New York City.

"Investigational Drugs in the Hospital Pharmacy," by Robert Farrier, M.D., Assistant Director of the Clinical Center.

"Nuclear Medicine Has Come of Age," by Mr. William Briner, Chief, Central Sterile Supply Service, Pharmacy Department, National Institutes of Health.

Massachusetts Society

The Massachusetts Society of Hospital Pharmacists presented an Educational-Refresher type program for its December 9 meeting, held at Peter Bent Brigham Hospital in Boston.

The theme of the meeting was "The Problems in the Physical Layout of a New Hospital or the Renovation of an Old Hospital Pharmacy." The interest shown was directly proportional to the length of the title. The program was presented as a panel discussion with three panelists representing the various size hospitals. Discussing the problems from the view-point of the large hospital, was Mr. John Murphy, of the Massachusetts General Hospital; Dr. William Hassan of Peter Bent Brigham Hospital represented the medium size hospital; and the considerations of the small hospital were discussed by Mr. Nathan Bornstein of the Winchester Hospital. The presentation was based on the generalities of space available versus work load rather than trying to solve any specific problem of an individual nature, and as a result was well received.

CONTINUED ON PAGE 40

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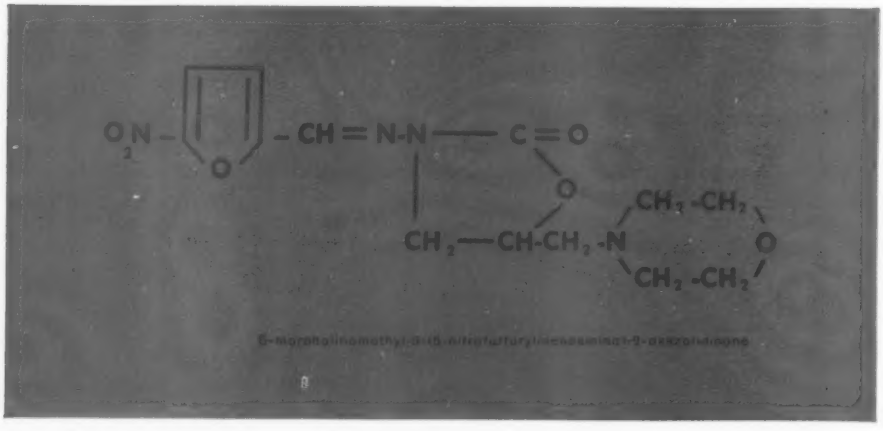

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Organism	*Sensitive*	*Resistant*	*% Sensitive*
Staphylococci*	181	1	99.4
Streptococci	65	1	98.5
D. pneumoniae	14	0	100.0
Coliforms	34	3	91.8
Proteus	5	5	50.0
A. aerogenes	8	0	100.0
Ps. aeruginosa	5	4	55.5

*Includes many strains resistant to antibiotics.

As with other nitrofuran compounds, development of bacterial resistance is negligible.

Clinically, ALTAFUR has proven most effective in the treatment of a variety of conditions including *pulmonary infections (pneumonia, empyema, bronchiolitis), upper respiratory tract infections, abscesses, cellulitis, pyodermas, septicemia/bacteremia and various wound infections.* ALTAFUR has produced cures in 75% of cases, and significant improvement in 10%.

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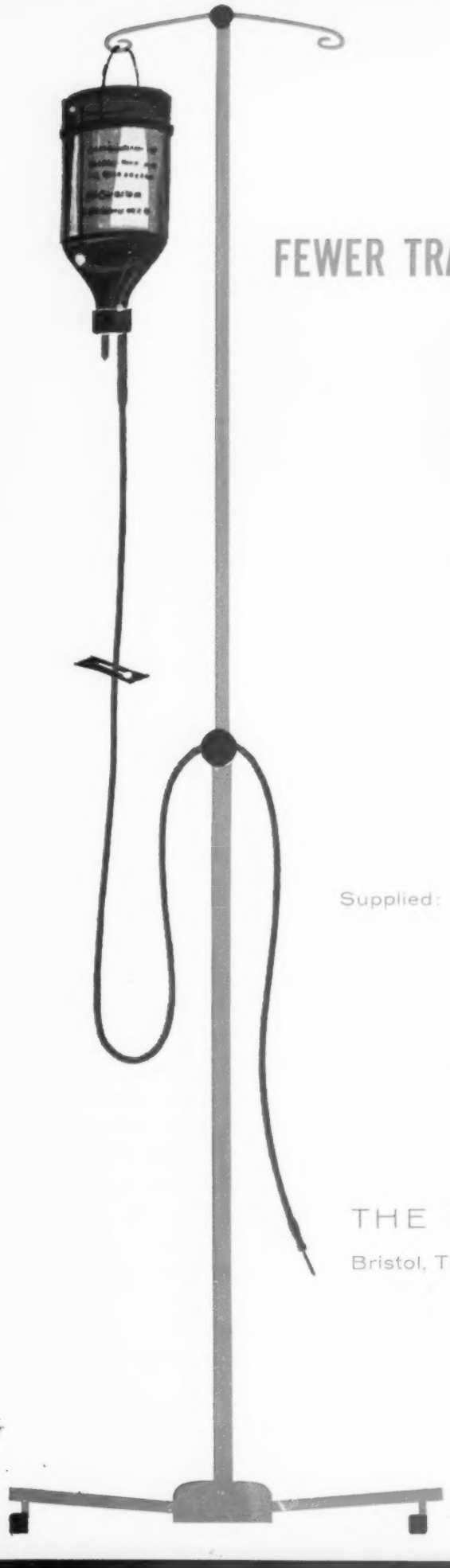

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1. 1958 Report of American Red Cross Joint Blood Council
2. References and detailed literature available on request.

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Michigan Society

The Michigan Society of Hospital Pharmacists met at the United States Public Health Service Hospital in Detroit on November 19.

Dr. Robert Y. Katase, M.D., Chief of Pathology, U.S.P.H.S. Hospital, was the featured speaker for the evening. Dr. Katase spoke on the "Experiences in the Medical Examiners Office."

New Jersey Society

The November meeting of the New Jersey Society of Hospital Pharmacists was held at the All Souls Hospital in Morristown. A buffet supper preceded the meeting.

Dr. Catherine Roth of Winthrop Laboratories was the guest speaker for the evening. She gave an informative talk on tranquilizers, including their similarities of action, indications for use, and side effects. Following her talk, Dr. Roth answered questions from the group.

During the business meeting which followed, Mr. Eugene Von Stanley, President of the Society, read a transcript of the discussion in the House of Delegates of the American Pharmaceutical Association which resulted in the passing of a resolution opposing the filling of outpatient prescriptions by hospital pharmacies. It was the feeling of the members present that there are differences in the understanding of the meaning of the term "outpatient department." A motion was made and passed that the Executive Committee of the New Jersey Society prepare a letter explaining the operation of a hospital outpatient department, and submit it for publication in the *Journal of the New Jersey Pharmaceutical Association.*

Greater New York Chapter

The regular monthly meeting of the Greater New York Chapter of the American Society of Hospital Pharmacists was held on November 17 at St. Clare's Hospital in New York City.

A questionnaire on proposed projects for the chapter was discussed. The members agreed that "Departmental Organization" and "Sources of Pharmaceutical Supplies" would be practical projects for the chapter.

The discussion for the evening was based on the topic to be considered by the New York State Hospital Pharmacists' Council at its next meeting—"Definitions and Suggested Pharmaceutical Procedures for Handling Drugs in Hospitals." While many of the definitions and procedures met with the approval of the group, some of the recommendations were questioned. These questions will be submitted to the Council for clarification at their next meeting.

Southeastern New York Chapter

The regular meeting of the Southeastern New York State Chapter of the American Society of Hospital Pharmacists was held on October 22 at the Mt. Sinai Hospital in New York City.

A report was heard on the activities of the New York State Hospital Pharmacy Council. The Constitution and By-Laws of this group were presented for consideration and ratification by the local Society. There was also discussion on the definitions and procedures used in hospital pharmacy that are to be presented to the State Board of Pharmacy.

Additional discussion during the business meeting concerned the selection of candidates for office by the Nominating Committee. It was recommended that the Constitution and By-Laws of the local Society be amended to state that the Nominating Committee submit two names for each office instead of just one name. This matter is being considered by the Executive Committee.

The program for the evening was presented by Dr. Richard Shoemaker of Pfizer Laboratories who spoke on the "History of Fermentation and Current Application in Pharmaceutical Manufacture."

The Lenox Hill Hospital was host to the November 17 meeting of the Southeastern New York State Chapter of the American Society of Hospital Pharmacists. A special guest at this meeting was Mr. Seyoun Bekele, Chief Pharmacist of the Ministry of Public Health of Ethiopia.

The discussion on the Constitution and By-Laws of the New York State Hospital Pharmacists Council was reopened. The members ratified the Constitution as written, with the provision that a section on parliamentary procedure be added to it.

The program for the evening was a "Problem Clinic" moderated by Mr. Alfred Rosenberg, Program Chairman. Included among the problems presented and discussed were: What is the Value of Pharmaceutical Displays; What Methods Can Be Used to Disseminate Medical Information to Staff Pharmacists; and The Pharmacy Bulletin as an Intra-Hospital Educational Tool.

Northeastern New York Society

The November meeting of the Northeastern New York Society of Hospital Pharmacists was held at the Petit Paris Restaurant in Albany. Mr. Louis Jeffrey presided at the meeting.

The program for the evening was presented by the Schering Corporation. Mr. Arthur Schmidt, Manager of the Hospital Sales Division of Schering, spoke on the research and use of oral fungicidal agents. Mr. Schmidt illustrated the subject with a film.

In the business meeting that followed, a report on the Annual Christmas Party was given.

Akron Area Society

A regular meeting of the Akron Area Society of Hospital Pharmacists was held on November 10 at the Akron General Hospital.

Dr. G. K. Parkes of Akron General Hospital was the speaker for the evening. He presented an outline of the disaster plan for Akron General Hospital in event of a major disaster. In the discussion period that followed, many questions were raised regarding the use of personnel, particularly interns, and the labeling of prescriptions.

Oklahoma Society

The Sixth Annual Convention of the Oklahoma Society of Hospital Pharmacists was held at the Hotel Mayo in Tulsa on November 5. Mr. Raymond Crews, President of the Oklahoma Hospital Association, gave the welcoming address and brought greetings from his association.

The first speaker on the program was Mr. Vernon Trygstad, President of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS. Mr. Trygstad spoke on "What's Ahead for Hospital Pharmacy." Other speakers and topics heard in the morning session were:

"Hospital Administrator-Pharmacist's Relation," by Mr. Robert Fitzimmons, USPHS, Administrative Officer, Indian Hospital, Talihina.

"ARB, Rx by Generic Name and Hospital Formulary," by Mr. E. W. Griffith of Oklahoma City.

At the luncheon, the principal address was given by Mr. Robert S. Birk of Oklahoma City. His topic was "The Glass House We Live In—The Example We Set."

During the afternoon session, the members heard a presentation by Sister Mary Rosina, O.S.F., Director of the School of Nursing, St. Anthony Hospital, Oklahoma City, who spoke on "The Pharmacist, Prescriptions, and Public

Participants in recent meeting of Oklahoma Society of Hospital Pharmacists included (l. to r.) ASHP President Vernon O. Trygstad; Robert S. Birk, Merck, Sharpe and Dohme, Oklahoma City; Verdi Mae Conely, Oklahoma University Alumni Association, Norman, Robert Fitzsimmons, U.S. Public Health Service Hospital, Talihina, Okla.; Sister M. Rosina, O.S.F., Director of the School of Nursing, St. Anthony Hospital, Oklahoma City; E. W. Griffith, Eli Lilly and Company, Oklahoma City; and Stokes E. Baggett, President of the Oklahoma Society

Relations." Another presentation at this session was "An Alumnus Looks at the Hospital Pharmacist," by Mrs. Verdi Mae Conley, President of the Oklahoma University Alumni Association.

The balance of the meeting was taken up with a business session at which time the reports of the various committees were heard, and the incoming officers were installed.

Greater Philadelphia Society

The regular monthly meeting of the Greater Philadelphia Hospital Pharmacists' Association was held on October 20 at the Philadelphia College of Pharmacy and Science.

The program for the evening was devoted to a panel of three hospital administrators, one from each of the various size hospitals, and two hospital pharmacists. Mr. Robert Simons, Program Chairman, was the moderator of the panel. An interesting and informative discussion gave light to the hospital administrator-pharmacist working relationship. Participating pharmacists and their topics were Mr. Sidney Kahn, Chief Pharmacist and Administrative Assistant, West Chester Memorial Hospital, who spoke on "What Does a Pharmacist Expect of an Administrator," and Mr. Robert Zykoski of the Lankenau Hospital, Philadelphia, whose title was "Your Hospital Pharmacist." The administrators taking part were Mr. C. Paxson, Hahnemann Hospital, Philadelphia, who discussed "What Does an Administrator Expect From His Pharmacy;" Mr. M. Abrams, Kent General Hospital, speaking on "Pharmacy Service in Small Hospitals;" and Mr. F. Larsen, Delaware Hospital, talking on "Can a Hospital Pharmacy Economically and Professionally Venture into the Manufacture of Large Volume Parenterals."

The conclusions reached by the panelists were that hospital administrators want pharmacists who are willing to contribute to the welfare of the hospital, and the well-trained, experienced hospital pharmacist will give high quality service. To carry on these functions in an efficient and economical manner, the pharmacist expects the proper personnel, adequate space allocation, and recognition from the administrator.

Western Pennsylvania

The Fifth Annual Hospital Pharmacy Seminar was held by the Western Pennsylvania Society of Hospital Pharmacists on October 22 at the St. Francis General Hospital and Rehabilitation Institute in Pittsburgh. Approximately 100 persons including hospital pharmacists, administrators, medical sales representatives, pharmacy students and faculty members were in attendance at the afternoon and evening sessions. The afternoon session, moderated by Dr. Joseph A. Bianculli, acting dean of the University of Pittsburgh School of Pharmacy, included a paper by Sister Mary Vera, R.S.M., Director of Pharmacy Service, Mercy Hospital, Buffalo, New York, who spoke about "Policy and Procedure Manuals;" a presentation by Grover C. Bowles, Director of Pharmacy Service, Baptist Memorial Hospital, Memphis, Tennessee, speaking on "Hospital Pharmacy—Then and Now;" and a discussion by Clifton J. Latiolais, Chief Pharmacist, University Hospital, Ohio State University Health Center, Columbus, on "Utilizing Statistics in Hospital Pharmacy Management." The format of the evening session, moderated by James E. Sandala, President of the Western Pennsylvania Society, was more informal and included a panel discussion "What's Your Problem?" which invited audience participation. Members of the panel included in addition to the above program participants, Sister M. Florentine, Chief Pharmacist, Mt. Carmel Hospital, Columbus, Ohio, and E. Burns Geiger, Pharmacy Service Manager, Pfizer Laboratories, Brooklyn, New York. Dr. George Archambault, being in the city for another meeting, joined the group for the evening session and contributed to the discussions.

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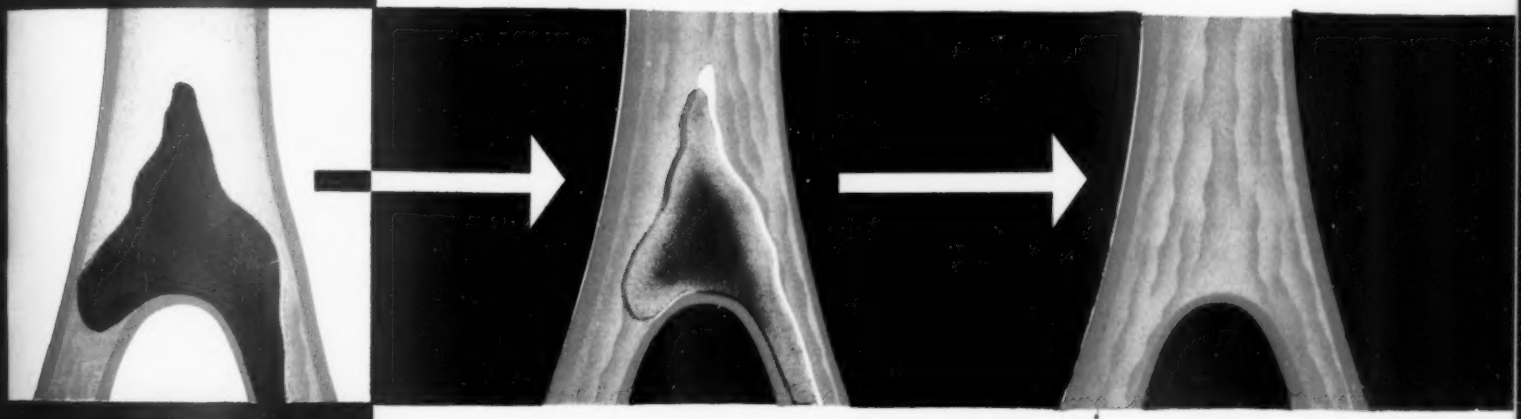
in thrombophlebitis and pulmonary embolism



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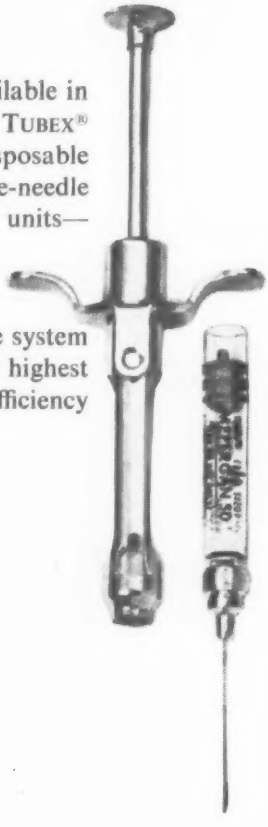

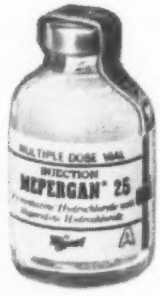

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Dear Sirs:

Comment on "Recovery Unlimited"

DEAR SIRS: I would like to make a few supplementary comments in regards to the article by Austin Smith (*Recovery Unlimited,* November, 1959).

As a representative of the pharmaceutical manufacturers' branch of the "health team" (or "health corps," if you will), Dr. Smith is perhaps a little more biased in his thinking than he would like to admit. Although I cannot and would not deny that the American drug industry has made and is making incomparable advances in chemotherapy, I resent the implication of semi-philanthropy. The average of seven percent which the drug industry spends on research indubitably exceeds that expended by the tobacco and liquor industries. However, my point is that this seven percent is being spent for the simple reason of business survival by the individual companies in a competitive market and not as a sacred investment in the future health of the human race (even though the latter is an inseparable by-product thereof). Research for the components of the drug industry is as necessary for their survival as advertising is to the members of the tobacco industry. To take credit for the advances in chemotherapy is the right of the drug industry and more praise is due them for their continuing efforts. Nevertheless, honesty would seem to require statement of the simple fact that a small amount of self interest is involved in their holy crusade.

I would like to suggest a fallacy in comparing the duplication of drug brands to ". . . more than one make of car, or one make of shoes or one brand of shirts, or ties, or handkerchiefs, or canned peaches or marmalade or coffee . . ." To restrict the analogy to cars, it seems to me that there is a distinct difference between three brands of dexamethasone (or three brands of hydrochlorothiazide) and three brands of cars. In one case, the drugs, you have three brands of IDENTICAL composition; in the other case, the cars, you have three brands of DISSIMILAR composition. The analogy of the three cars could be used in explaining three types of diuretics—benzydroflumethiazide, chlorothiazide, and hydrochlorothiazide. The latter is ramification, not duplication, and is not generally criticized or misunderstood.

I offer these suggestions as a member of the "health corps" who has unbounded admiration for the drug industry as a whole.

WILLIAM A. DILLON, *Staff Pharmacist*

Huron Road Hospital
13951 Terrace Road
Cleveland 12, Ohio

Appreciation for Tribute

DEAR SIRS: Concerning the death of J. Robert Cathcart, kindly accept my appreciation for your tribute to this man.

I consider myself fortunate to have been associated with him during the last years of his life as his assistant, student, and most important, his friend.

Future material contribution by J. Robert Cathcart will be lost to us but perhaps his inspiring devotion and drive in spite of sometimes insurmountable obstacles will remain in our SOCIETY.

MARTIN S. GOLDSTEIN, *Chief Pharmacist*

The Montefiore Hospital
Fifth Avenue at Darragh
Pittsburgh 13, Pa.

Note: Texas Pharmacy Registrants

DEAR SIRS: We are endeavoring to inform all Texas Pharmacy Registrants that the Texas Pharmacy Law was amended and affects all Texas Pharmacists in the Federal Services with respect to paying their renewal fee for their pharmacist license.

Before August 11, 1959 the State of Texas did not require their pharmacists to pay a renewal fee for their license if they were in the Federal Services. As of August 11, 1959 the amended Pharmacy Law does require *all* pharmacists to pay $10 for the renewal of their license. The fee is due January 1, 1960 and becomes delinquent if not paid before March 1, 1960 and the penalty for delinquency is $10.

We would appreciate it if you would publish this change in your publication, thereby assisting us to inform the Texas Pharmacists in the Federal Services.

We thank you for your fine cooperation.

J. H. ARNETTE, *Secretary*

Texas State Board of Pharmacy
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by DON E. FRANCKE

The Law of Reasonableness Applies

► SINCE I AM NOT AN ATTORNEY, I AM NOT GOING TO try to discuss the principle of prior consent from a legal point of view. Rather, I shall discuss it from a professional viewpoint and show that it meets the law of reasonableness.

However, first let us clarify what we mean by prior consent. Webster defines consent as, "a capable, deliberate, and voluntary assent or agreement to, or concurrence in, some act of purpose. . ." Prior consent, then, would be consent given prior to the act.

In this discussion, we are applying the principle of prior consent to that system employed by hospitals, under which the members of the medical staff authorize the pharmacist to dispense drugs by their non-proprietary names, regardless of the names used by the physicians to prescribe the drugs. This authorization usually arises as the result of a written recommendation from the Pharmacy and Therapeutics Committee to the medical staff of the hospital. The medical staff has the authority to alter, amend, veto or approve the recommendation. If the recommendation is approved, it then becomes a written policy of the hospital. If it is vetoed and the pharmacist dispenses a brand different from that prescribed without the physician's consent, he is guilty of substitution.

The point at issue when we talk about the consent of the physician, as applied to hospital practice, is really prior consent. In any event, I know of no pharmacist in any branch of the profession who would dispute the statement that every pharmacist has an inalienable right, when one brand of a drug is prescribed, to ask the physician for his authorization to dispense another brand which he may have in stock.

However, the profession as a whole, other than hospital pharmacists, thinks of the physician's consent as an authorization obtained after an individual prescription is received by the pharmacist. This thinking, I believe, is based upon the differences in the relationship between physicians and pharmacists in retail practice in contrast to the relationship existing in hospital practice. Retail pharmacists do maintain a professional relationship with physicians but it lacks the formal, organizational aspects which exist between physicians and pharmacists in hospitals where the pharmacist is a member of the Pharmacy and Therapeutics Committee. This is a committee of the medical staff which represents the official, organizational line of communication and liaison between the medical staff and the pharmacy department. It assists in the formulation of broad professional policies regarding essentially all matters relating to drugs in hospitals. Thus, it is easy to understand why hospital pharmacists view the matter of physicians' consent from a different vantage point. It is natural that they should; they are in an entirely different position than their colleagues in retail practice. Certainly all would agree that a pharmacist who can communicate with a few to several hundred physicians as a single group is in a different position than one who must communicate individually with each physician. Or one may state the advantage in a different manner by saying that a group of physicians may more easily communicate with one pharmacist in a hospital, where all are in daily contact, than it can with pharmacists scattered throughout the community.

Hospital pharmacists have, in fact, no difficulty accepting the definition of substitution published by the National Pharmaceutical Council. This definition reads: "Substitution is the dispensing of a different drug or brand of drug in place of the drug or brand of drug ordered or prescribed without the express permission of the prescribing physician."[1] Hospital pharmacists maintain they have obtained the "express permission of the prescribing physician" within the meaning of this definition and are in no wise engaged in a practice of substitution.

Hospital pharmacists believe that the physician's consent is obtained in a manner which satisfies the law of reasonableness. Authorization must first be recommended by a committee of the medical staff, it must then be approved by the medical staff itself, and it must finally be approved by the director of the hospital. In addition, members of the medical staff are in a position to provide exceptions to any rule adopted and in this way preserve the professional prerogative of those physicians who may believe that in certain instances it is desirable for a patient to have a specific brand of a drug.

Thus, hospital pharmacists believe they are in a strong legal and ethical position in this matter and seriously question whether a board of pharmacy could successfully charge a hospital pharmacist with substitution, if prior consent to dispense drugs under their non-proprietary names is granted by the members of the medical staff. They point to the fact that the consent obtained under these conditions is "a capable, deliberate and voluntary assent or agreement to, or concurrence in, some act or purpose." The principle of prior consent is a reasonable principle which has the support of physicians, administrators, and hospital pharmacists.

Adapted from a paper entitled "The Principle of Prior Consent in the Formulary System," presented before the Pharmacy Section, American Association for the Advancement of Science, Chicago, December 1959.

1. *Drug Trade News, 30*:45 (Nov. 21) 1955.

STABILITY & STABILIZATION OF MEDICAMENTS

1. Stability of Medicaments

by SVEND AAGE SCHOU

► I FEEL THE INTEREST THE SCIENTIFIC SECTION has taken in the problem of "Stability and stabilisation of medicaments" to be a reward to skillful colleagues all over the world for the persevering work which through the last decades they have devoted to this important problem.

As recently as during the first decades of our century the pharmaceutical preparations were chiefly rather complex systems if not preparations from vegetable drugs. They were considered to be fully characterized by the raw material and the pharmacist's skill and in this was included that the final product was "stable," as far as one could see from the preparation's physical properties. The remedies in use nowadays are simpler and more rational. Very often our preparations contain one active component only, and we have simple methods for their evaluation, physical, chemical or biological. This being the case, we must of course take over the whole responsibility of the stability of the preparation. Only when the stability is known are we able to arrange the production according to consumption, whether in the industry or in the pharmacies.

The rapid development of the study of pharmaceutical preparations has created an increased interest in the problem of the stability, and this interest is based not only on the interest of pure medicine and

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Presented at the 19th F.I.P. International Congress of the Pharmaceutical Sciences, September 1959, Zurich, Switzerland.

pharmacy, but is due also to the fact that the problem of stability has far reaching financial implications.

An official interest came into the picture when in Sweden, now more than ten years ago, the Defence Ministry found out that morphine ampuls worth a total of over £3000 had to be rejected annually because of questionable stability. Hence a special committee for the study of the stability of pharmaceutical preparations was delegated to examine whether a rejection of this order of magnitude was really necessary, and it was shown that much money could be saved in a simple way.

In Denmark a committee for the stability of pharmaceutical preparations was established in 1949 by the Academy of Technical Sciences. The results obtained by this committee are to be found in a special report, copies of which I have the pleasure to be able to offer interested colleagues.

Definitions of Stability

I should like now to discuss briefly the difficulties involved in formulating a general definition of the term *stability*. Previously a pharmaceutical preparation was considered stable as long as no changes demonstrable by the senses had taken place, *i. e.* changes of smell, taste, color or consistency, the formation of a precipitate or a growth of microorganisms, whereas now—in addition to the still valid classical but somewhat vague demands—more specific demands are made, and attempts have been made to define the concept of stability in more direct accordance with the content of the active substance in the preparation.

With this in mind the stability of a pharmaceutical preparation could be defined as the period of time from the completion of the preparation and until it no longer fulfils the specifications of the pharmacopoeia. This definition would appear to be ideal on two conditions: 1) that all preparations were adopted by the pharmacopoeia, and 2) that the pharmacopoeia would—and could—contain detailed specifications concerning each preparation. Thus it appears now that a very considerable limitation exists in the applicability of the definition.

The following definition has advantages, but is not applicable in all cases. The stability of a pharmaceutical preparation is the period of time from the completion of the preparation and until the activity of the preparation has been reduced by a stated percentage of *e. g.* 10 percent.

If we combine the two definitions I do think we will have a practical definition. But to this point we will have to return later.

How is the present state of the stability question in our pharmacopoeias? Well, the various pharmacopoeias—with the exception of the British and the Danish—give surprisingly few directions concerning storage and stability of their preparations, the classical —and cheap—remark: "To be kept in a cool place, excluded from light in a well closed container" being the average standard in too many pharmacopoeias.

The American, the British and the Danish pharmacopoeias are in a way representative of three different ways of handling the stability problem, so we better have a look at them.

First I should like to say that studying the American pharmacopoeia one might easily get the impression, that it was the adoption of sera and vaccines in the pharmacopoeia which forced the problem of storage and the limitation of storage time into the pharmacopoeia literature. This is quite understandable as serologists and bacteriologists were the first —now more than fifty years ago—to realize the importance of the stability problem for the applicability of their "biological" products (sera and vaccines) in the therapy. As these pioneers in the question of stability entered into collaboration with the professional pharmacopoeia-authors, it was a matter of course that they insisted on the introduction of their well stated demands on storage conditions and storage limitations in the pharmacopoeias.

Another point which must force the pharmacopoeias to adopt a more active interest in the stability problem is the introduction of new and potent but often rather unstable substances in our therapeutic armamentarium. One gets the distinct impression that the potence of a number of the new therapeutics is connected in some way with their instability. Just as the vast potency of our new sources of atomic energy is closely connected with the instability of the radioactive substances.

Practically speaking this means that we have to learn to handle, to prepare and to store our unstable remedies in such a way that they will come into the hands of the patients or of the doctors with their potency intact. Well, this is and always was the essence of pharmacy. So we have to face these problems, they are not new, they are old as pharmacy itself, but now they force their way into practical pharmacy with an obviousness making it impossible to ignore them.

Some pharmacopoeias show this quite clearly. In several cases they now recognize the conspicuously unstable substances whereas the old, well known substances are still merely "kept protected from light, etc.," even if they are not too stable. We must now consider the stability problem as a whole. Regulations for the storage of sera and vaccines only do not satisfy a professional pharmaceutical conscience.

For the purpose of this lecture I prefer to include only 3 pharmacopoeias in the analysis, *viz.*, the American, the British and the Danish, each of these pharmacopoeias representing a special attitude towards the stability problem.

U. S. Pharmacopeia

The United States Pharmacopeia (U.S.P. XV, 1955) has quite obviously been forced to face the problem through the *"biological products."* In all of the 25 monographs dealing with sera, vaccines and blood-products a time limit is given—from 3 months (smallpox vaccine), 6 months, one year, two years, three years until 5 years (dried serum and dried plasma). But as soon as we turn to more classical chemicals and preparations it is obvious that the influence due to the "biologists" interest in the stability problem has been but slight. For only three *chemicals* a limited storage period is mentioned. And if we turn to the *pharmaceutical preparations* only 4 are to be found.

Table 1. U.S.P. XV, 1955

BIOLOGICAL PRODUCTS (EXAMPLES OUT OF *31* MONOGRAPHS)	
Diphtheria Antitoxin	1 year
Diphtheria Toxoid	2 years
Immune Serum Globulin	3 years
Insulin Injection	2 years
Pertussis Immune Human Serum	1 year
Pertussis Immune Human Serum, dried	5 years
Rabies Vaccine	6 months
Smallpox Vaccine	3 months
Tetanus Antitoxin (1 year, + 20%; 2 years, + 30%; 3 years, + 40%; 4 years, + 50%)	
Old Tuberculin	5 years
Typhoid and Paratyphoid Vaccine	18 months

Table 2. U.S.P. XV, 1955

Pharmaceutical Preparations	
Ergonovine Maleate Injection	2 years
Isoflurophate Ophthalmic Solution	2 years
Potassium Penicillin in Sterile Solution	3 days
Vinyl Ether (when opened)	48 hours
Water for Injection (NB.)	24 hours
CHEMICALS	
Oxophenarsine Hydrochloride	3 years
Tryparsamide	5 years
RADIOACTIVE PREPARATIONS	
Sodium Radio-iodide (I^{131}) Solution	half life 8 days

In addition to this I should like to show you a list out of 36 preparations, not a complete list but some selected monographs where I would have expected some sort of limitation.

Table 3. U.S.P. XV, 1955

NO LIMIT (SELECTED MONOGRAPHS—OUT OF *36* WHERE A LIMIT SHOULD BE EXPECTED)
Chloramphenicol Ophthalmic Ointment
Decavitamin Capsules
Decavitamin Tablets
Ergotamine Tartrate Injection
Glyceryl Trinitrate Tablets
Oxytocin Injection
Phenylephrine Hydrochloride Injection
Phenylephrine Hydrochloride Solution
Posterior Pituitary Injection
Procaine Hydrochloride and Epinephrine Injection
Vasopressin Injection
Water-miscible Vitamin A

The last group from this pharmacopoeia we have to examine is the *radioactive preparations* and these have as a matter of course statements of the half-life periods. Again an example of the stability forcing its way into the pharmacopoeia. On the whole the American pharmacopoeia sticks to the classical standpoint that as a preparation must at any time fullfil the demands of the pharmacopoeia it is not necessary to state a limited storage period. The responsibility concerning the activity of any preparation rests upon the manufacturer and/or the pharmacist; they have to undertake the responsibility for the stability. This view point is quite clear but rather troublesome for the practical pharmacy which is left to its fate without sufficient information.

Even if the justice of this viewpoint is open to discussion from a professional pharmaceutical point of view, it is in accordance with the whole attitude of this pharmacopoeia which is to formulate certain demands and for the rest leave it to the producer how to find a way to fullfil the demands. As already mentioned, this viewpoint is clear and must be respected—but it is troublesome.

The British Pharmacopoeia adopted a positive attitude towards the stability problem already in an earlier edition, and stated a limitation in time for the storage of certain preparations, or better it indicated the period of time for which the preparation "may be expected to retain its potency." This line has been followed up in the 1958 edition. I have the impression that originally the British pharmacopoeia also received its inspiration for the *"biological products"* as for 7 antitoxins and 16 vaccines (and the like) detailed information on storage conditions and a limitation in time are stated. From a pharmaceutical point of view it is more interesting that a limitation in time is to be found for *24 pharmaceutical preparations* comprising 20 injections, glyceryl trinitrate *tablets* and halibut liveroil *capsules*.

Table 4. British Pharmacopoeia 1958

Pharmaceutical Preparations		
Benzylpenicillin Injection	14 days	<4°
Dextran Sulphate Injection	"at least 2 years"	
Dihydrostreptomycin Sulphate Injection	1 month	<4°
Glyceryl Trinitrate Tablets	"1 year"	
Halibut-liver Oil Capsules	"3 years"	
Heparin Injection	"3 years"	
Insulin Injection	"2 years"	as low a temp. as possible above its freezing point
Other Insulin Preparations	"2 years"	
Oxytetracycline and Procaine Injection	4 days	<4°
Oxytetracycline Injection	48 hours	<4°
Oxytocin Injection	"18 months"	temp. as Insulin
Fortified Procaine Penicillin Injection	4 days	<4°
Streptomycin Sulphate Injection	"1 year"	cool place
Suxamethonium Chloride Injection	"2 years"	<4°
Tetracycline and Procaine Injection	"24 hours"	
Tetracycline Injection	"24 hours"	
Vasopressin Injection	"18 months"	temp. as Insulin
Vinyl Ether, when opened used within	48 hours	
Corticotrophin	"2 years"	
Corticotrophin Injection	within 1 month	2°-4°

It is worth noticing that this list includes preparations for which U.S.P. does not mention any limitation, *e.g.*, the glyceryl trinitrate tablets, oxytocin and vasopressin injection. On the other hand, the British pharmacopoeia does not mention any limitation for quite a number of injections where a limitation might be expected.

Table 5. British Pharmacopoeia 1958

NO LIMIT (selected monographs out of 39 where a limit should be expected)
Cortisone Injection (Asept.)
Ergometrine Injection (A.)
Ergotamine Injection (A.)
Hydrocortisone Injection
Lignocaine and Adrenaline Injection (A.)
Mersalyl Injection (H.w.B. or F.)
Methylergometrine Injection (—O_2; A.)
Procaine and Adrenaline Injection (100°-30')

Notice especially cortisone, ergometrine, lignocaine and adrenaline, mersalyl, methylergometrine and procaine and adrenaline injections.

When halibut liver oil and vitamin A and D concentrates can be stored "as long as it fullfils the standards given in the pharmacopoeia" it is understandable that a control of the activity of these preparations is limited to laboratories with special equipment, but I do feel that a limitation would be more in the interests of the pharmacy as well as of the customers. The fact that a preparation such as surgical chlorinated soda solution has no limitation I do not understand at all.

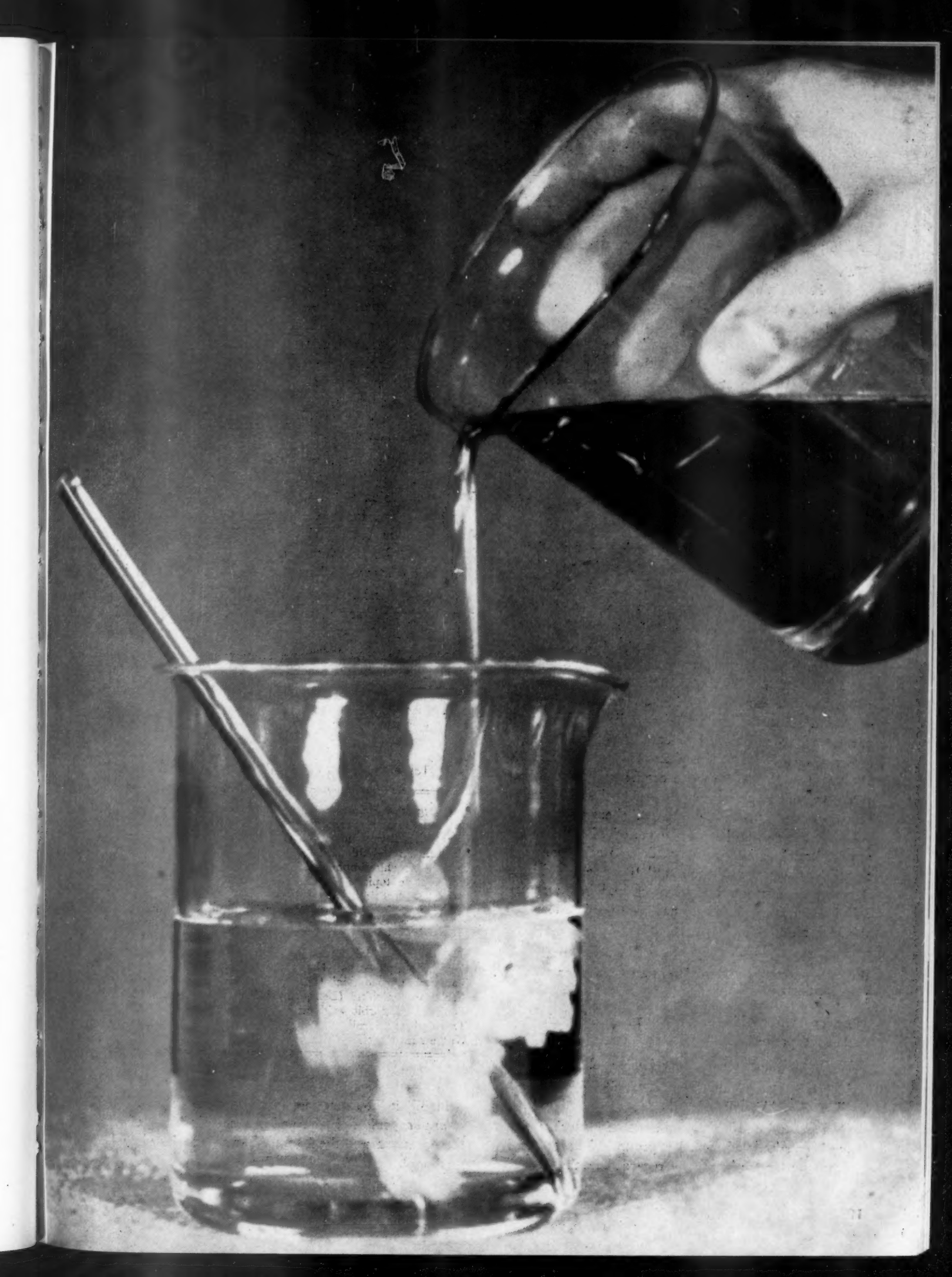
Table 6. British Pharmacopoeia 1958

Radioactive Preparations		
Sodium Radio-iodine (^{131}I) Injection	Half-life	8 days
Sodium Radio-iodine (^{131}I) Solution	Half-life	8 days
Sodium Radiophosphate (^{32}P) Injection (Autoclaving $Q_{10°}=1$)	Half-life	14 days
"Biological Products"		
Antitoxins	(7)	
Vaccines	(16)	
(Detailed information on storage conditions and time-limit)		

Table 7. Ph. Dan. 1948 Remedies for which a definite keeping-time has been stipulated

THE SPECIFIED PERIODS ARE VALID FOR KEEPING AT ROOM TEMPERATURE. IF STORED IN WELL-CLOSED OR AIRTIGHT CONTAINERS AT 5° C OR BELOW THE INDICATED KEEPING-TIME IS DOUBLED

	Remarks	Limit for keeping-time
Acetum sabadillae	store in a cool place	6 months
Acidum ascorbicum	in injections containing 0.45 g Sodium bicarbonate per gram ascorbic acid	6 months
Adrenalini bitartras	dissolved	1 year
Adrenalinum	dissolved	1 year
Adrenoni hydrochloridum.	dissolved	1 year
Aneurini hydrochloridum.	solution for oral use, containing 1% 0.1 n HCl and 20% alcohol	3 months
Apomorphini hydrochloridum	in solution containing 0.3% 0.1 n HCl and 0.1% Sodium pyrosulphite in ampuls	1 year
Aqua sterilisata	in Erlenmeyers and bottles	2 months
Atropini sulfas	in solutions containing less than 0.1% 0.1 n HCl	1 year
Calciferolum solutum ...	store at low temperature for instance in a refrigerator (4° C)	1 year
Calciferolum solutum concentratum	store at low temperature for instance in a refrigerator (4° C)	1 year
Calcii silicas cum belladonna		1 month
Capsulae extracti filicis ..	stored in a cool place	1 year
Cincaini hydrochloridum .	in solution	1 year
Concentratum A-vitamini .	store at low temperature for instance in a refrigerator (4° C)	1 year
Diemalnatrium	dissolved	6 months
Emulsio penticidi		1 month
Extractum filicis	stored in a cool place	1 year



That 9 preparations "must be used immediately after preparation" is obvious for most of them. How Amethocaine injection (Tetracaine) can be included I do not understand. We, of the Danish pharmacopoeia, believe this preparation to be stable for 1 year. Towards the radioactive substances the attitude of the British pharmacopoeia is the natural one: indication of the half-life period.

Taken as a whole it must be said the British pharmacopoeia has not only faced the stability problem but has early realised its importance and is on its way to build up a reliable system in which new facts, new experimental results can easily be incorporated. The essence of the attitude of the British pharmacopoeia towards the stability problem may be summarized as follow: Indication of the time the preparation may be expected to retain its potency under certain, given, storage conditions. On the other hand, no attempt is made in the way of a generalization of the problem.

Danish Pharmacopoeia

The Danish Pharmacopoeia has adopted a third attitude towards the stability problem. In the 1948 edition of this pharmacopoeia we tried to build up a more comprehensive system, based on a series of studies of the stability of certain pharmaceutical preparations. Not all of the storage periods could be based on experimental results, and furthermore it would also appear to be desirable to obtain results more generally applicable for the elucidation of the principles of decomposition of the active ingredients in the preparations in question. It had been considered possible to arrive at a listing in the pharmacopoeia of the rate constant and the temperature coefficient for temperatures around room temperature for the destructive processes taking place in the official preparations, thus allowing the calculation of the period of stability for any arbitrary temperature, *e.g.*, defined as above mentioned by the period of time until 10 percent had been decomposed. But to this point we had better return a little later, as so far it has not been possible to reach this high aim.

To build up the whole system it was necessary—in the classical way—to differentiate three groups of preparations:

A. Remedies which shall be prepared each time they are prescribed.

B. Preparations which may be stored for a short time, only this vague term being defined or better explained as well as possible.

C. Preparations for which a definite storing time has been stipulated. This last group is the most significant by far, and must be regarded as the first attempt to regulate the storage problem and to bring it into accordance with our practical and theoretical knowledge.

The first of these groups today comprises 61 preparations, the second 50 and the last and most interesting group 104 preparations. From table 7 you will get an impression of the way we have grouped the preparations in question.

About half of the preparations are injections and eyedrops for a number of which we have had—from sterilization experiments—at least some experimental data on which to build the classification. But for a good deal of the preparations we have had to build merely on a generalization using the temperature coefficient, the Q_{10}°, for the process in question. To judge the permissibility of this whole system we will have to look into the theoretical basis more closely. But already I should like to add, that the system has by now been practised for about 10 years and it is so widely adopted in practice that all criticism has died down. The inconvenience caused by the comparatively short storage periods for the practical pharmacy has been fully compensated by the satisfaction the profession has gained, the satisfaction, even pride of the preparations being known to be as potent as they should be.

I should further like to add, that the semi-official formulas given out by the Danish Pharmaceutical Society (Danmarks Apotekerforening)—the so-called DAK formulas—loyally and as a matter of fact have followed the way indicated in the pharmacopoeia. For 17 preparations definite storage times are given in this codex.

Table 8. DAK Preparations 1950—1959

Conspergens topicini	1 year
Guttae adetamini fortiores aquosae	3 months
Injectabile B-combini	3 months
Linimentum polythionatis	6 months
Oculentum chloramphenicoli	2 years
Oculoguttae topicini	14 days
Oriblettae topicini	6 months
Otoguttae chloramphenicoli (propylenglycol)	1 month
Pilulae A-D-vitamini	8 months
Solutio topicini	14 days
Syrupus B-combini	3 months
Tablettae diplonitroli (NB)	1 year
Tablettae nitrocombini (NB)	1 year
Tablettae penicillini (Benzylpenicillin)	6 months
Tonicum (Ascorbic acid etc.)	3 months
Trochisci calciferoli	1 year
Ungrentum topicini	6 months

Finally it should be mentioned that the *International Pharmacopoeia* has adopted the specifications of the the American and the British pharmacopoeias virtually unaltered.

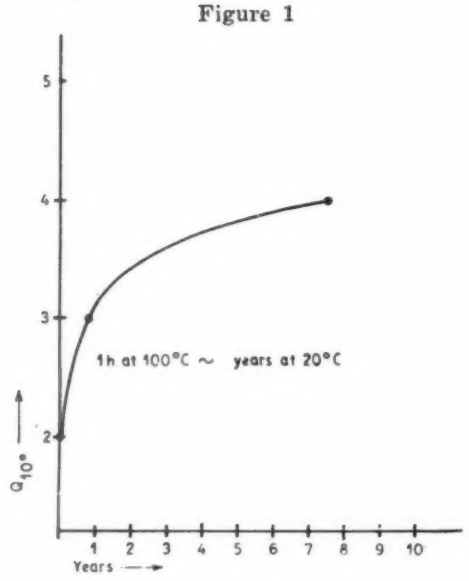
Computation of Stability

In order to establish certain definite periods of stability for a large number of preparations included in Ph. Dan. '48 we have resorted to our available knowledge considering the destructive effect of heat sterilization on various substances. On this basis an attempt has been made to compute the stability at room temperature by using a probable temperature coefficient in addition to a fair amount of "estimating." This procedure may be said to represent an application of accelerated experiments. This type of experiment, *i.e.*, experiments at a temperature which is higher than the storage temperature, is of great value when the temperature interval involved in the estimation is not too extensive, and when the temperature coefficient is known within this temperature interval. Even a brief consideration of the influence of the temperature coefficient is sufficient to show the necessity of determining this quality with a fairly high degree of accuracy.

The significance of the temperature coefficient used, *viz.*, whether 2, 3 or 4 as computed from a temperature of sterilization to room temperature, appears from the following figure which gives the period of time at room temperature equalling heat sterilization for temperature coefficients of 2, 3 or 4.

The figure shows clearly the importance of an accurate determination of the temperature cofficient when accelerated experiments are used, as well as the importance of conducting stability experiments at the storage temperature proper.

Figure 1



In 1889 Svante Arrhenius gave the following theoretical basis for the relation between temperature and the rate of the reaction:

$$\log k = \frac{E_A}{R} \cdot \frac{1}{T} + q,$$

T being the absolute temperature, q a constant independent of temperature, R the gas constant and E_A being the "critical increment" of Arrhenius, or the activation energy as we now call it, *i.e.* a factor increasing with temperature. Graphically the relation between the rate of the reaction (—log k) and the temperature $\frac{1}{T}$ is represented by a straight line, its inclination being expressed by $\frac{E_A}{R}$

As early as 1902 Arrhenius, in collaboration with Th. Madsen, showed that processes concerning toxins and antitoxins, *i.e.*, substances which may very well be considered to be remedies, could be treated according to the usual physico-chemical laws; and in 1909 Th. Madsen and Osv. Streng showed that the effect of temperature on the destruction of antibodies could be expressed by means of the Arrhenius' equation. Over the years this has been shown for other remedies as well, thus in 1928 by Aug. Krogh and A. Hemmingsen for insulin, and finally it should be mentioned that R. Brodersen, 1947, showed the validity of Arrhenius' equation for aqueous solutions of penicillin. Simultaneously Brodersen pointed out the necessity of considering the important factor of the considerable shift in the C_H+ or the $C_{OH}-$ induced by temperature. The latter is another example of the fact that calculations involving sizable temperature intervals provide considerable sources of errors. A good part of the work involved in using accelerated experiments consists in finding and eliminating these sources of errors. In the case of the basic experiments described concerning the destruction of certain important pharmaceutical preparations as a function of time (the stability) it was possible to treat the reaction as a first order reaction; but this will be discussed in detail subsequently.

Determining Factors

Thus the determining factor for a more theoretical treatment of the problem of stability is the question of whether or not it is possible to treat the processes causing the deterioration of the potency of pharma-

ceutical preparations according to the ordinary physico-chemical laws for the rates of reactions. On the whole, the answer must be yes, but of course the variety of the pharmaceutical preparations as seen from a physico-chemical point of view forces us to make certain simplifications.

First we have to consider the importance of the state of matter for the possibility of a reaction taking place and for the rate of reaction. If we try to classify our pharmaceutical preparations from a physico-chemical point of view we must at least consider the big difference in reaction possibilities if we have:

(a) Solid heterogenous systems (as we have them in powders and tablets),

(b) Liquid heterogeneous systems (as in suspensions, oil suspensions and ointments),

(c) Liquid homogenous systems (solutions, injections, etc.).

It is well known that within the first group the reaction possibility is poor, hence it follows that in this group we must expect the preparations to be stable. On the other hand, we have examples of unstable preparations even in this group. Only two examples shall be mentioned. An antacid much used in Denmark, Pulvis Alkalinus cum Hyoscyamo, a mixture of sodium bicarbonate, magnesium carbonate and dry extract of hyoscyamus, has shown so varied a stability, or rather such distinct instability, that the Danish pharmacopoeia has had to estimate the permissible storage period to one month only. Even if the preparation is a solid one the basic substances can obviously catalyze the hydrolyzation of the tropa-alkaloids. This process must be a function of the humidity, and the reaction must take place in the surface layers where the humidity is adsorbed to the solid substances. This shows clearly that the stability problem in this case is dependent on more or less unknown variables and thus cannot be treated in a simple scientific way. The stability of preparations of this type must be investigated empirically—under conditions as constant as possible—and the conclusions must be drawn with great care, the reaction possibilities being ambiguous.

(a) *Tablets* are generally known to be stable, again due to the solid state. On the other hand examples of unstable tablets are well known and a few have been subjected to a more detailed investigation. Today one example only will be mentioned. The stability of Glyceryl Trinitrate Tablets has been discussed for years, and as already mentioned the British pharmacopoeia has stated the permissible storage period to be one year.

We now know that the stability of these tablets is dependent on various factors. Frst, the possible evaporation of the glyceryl trinitrate will involve a loss of active substance and in addition to this, unknown reactions leading to the formation of nitrite and possibly also to the formation of esters other than the trinitrate will take place. To treat such a complicated system scientifically is not possible today. Again we must state that the problem must be treated empirically and in such a way that the most important factors in connection with the stability can be controlled. In this special case the presence of any organic material in the storing and packing of the tablets must be avoided, *i.e.*, cork, cotton, paper and in particular rubber and polyethylene have shown to lead to a reduction of up to 60 percent in one year. But if these substances are avoided the tablets can be stored for one year—in glass or metal containers—with the reduction limited to less than 10 percent.

(b) *Liquid heterogenous systems* represented by *e.g.*, suspensions (aqueous or oily) and ointments are as difficult to treat from a scientific point of view as are the solid systems. Each individual case must be investigated empirically and a generalization is seldom permissible. In this case also the reactions must take place on the surface of the active substance, this being the suspended component. Particle size, solubility in the medium, presence of catalysts, etc., are factors so decisive for the stability that it is rather difficult to treat the problem in a general way. One point should be mentioned. The activity of the parenteral suspensions of steroids now widely used is dependent on the particle size—the surface area—of the chemical.

The preparation often being a suspension of crystals of a claimed special particle size (micronized particles) in a saturated solution of the substance will, due to the interaction between the crystal-surface and the solution, continuously change in the particle size. The crystals will usually grow. This important problem has as far as I know not yet been investigated.

(c) *The liquid homogeneous systems,* the solutions, so far the most important preparations and the preparations where we must expect and do indeed find the unstable preparations, we are able to handle in a more theoretical way. The decrease in the activity, that is to say the rate at which the active substance is transformed or destroyed as a function of time and temperature can, at least if we consider the aqueous systems, be treated in accordance with the simple laws of physical chemistry.

It is out of the question in this lecture to discuss the physico-chemical basis for the stability problem in detail. A few important points only shall be mentioned.

Accelerated Stability Studies

When a molecule reacts it is because enough energy is supplied—the activation energy being expressed by the Ea of the Arrhenius equation—to activate it from the stable, or rather metastable, state. This may take place without the molecule in question colliding with another one or with other types of molecules, but in most cases a collision between the reacting molecules is necessary. The reactions are termed monomolecular, bimolecular and trimolecular according to the number of molecules participating.

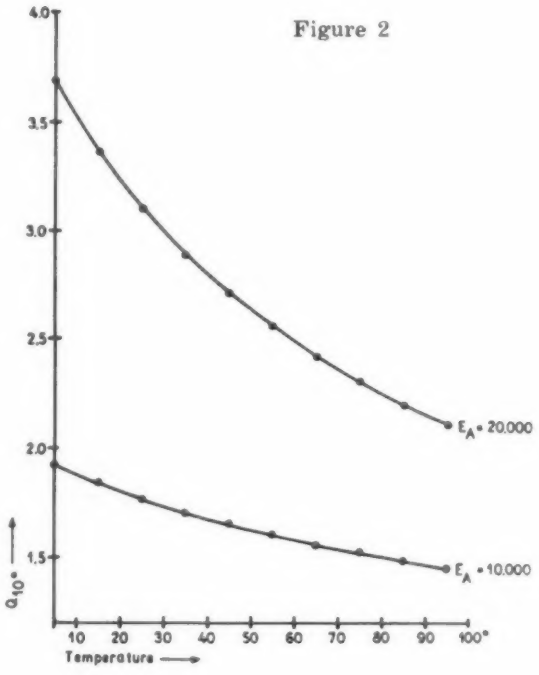
Thus the energy of activation is closely related to the rate of the reaction taking place. If the energy of activation is of an order of magnitude of 1000 cal./mol. the reaction proceeds almost instantaneously at room temperature. If the energy of activation is of an order of 10,000-20,000 the reaction proceeds at a measurable rate at room temperature, although at the highest energy of activation the period becomes very long. Reactions proceeding at room temperature at a suitable, measurable rate have an approximate Q_{10}^0 of about 2, corresponding to an activation energy of 13,000 cal./mol. At higher activation energies the Q_{10}^0 exceeds 2 at room temperature.

In the case of accelerated experiments, *i.e.*, experiments carried out at higher temperatures, if the rate of the reaction at room temperature is too slow to allow the experiment to be concluded within a reasonable period of time, one has frequently assumed the Q_{10}^0 to be fairly constant from the temperature of the experiment and down to the possible storage temperature. But the Q_{10}^0 is not constant. It decreases somewhat with increasing temperature. Hence the results obtained become misleading if the same factor is used over too wide a range of temperature. In figure 2 the variation in the Q_{10}^0 is seen as a function of temperature and in figure 3 as an example of the error committed by assuming the Q_{10}^0 to be constant within the range most frequently of interest to pharmaceutical research, *i.e.*, from 100° C. (sterilization temperature) and down to room temperature (20° C.), the ordinate being the factor with which we have to multiply the time at 100° C. to get the time at 20° C. Simultaneously, it is possible from this figure to estimate the range within which it is permissible—without committing to serious errors—to assume the Q_{10}^0 to be constant (dotted lines).

When the active substance of one of our preparations is transformed its concentration changes continuously—*i.e.*, its concentration decreases whereas the concentration of the product—or products—of the reaction increases continuously. It is therefore necessary to consider the relation between concentration and the rate of the reaction.

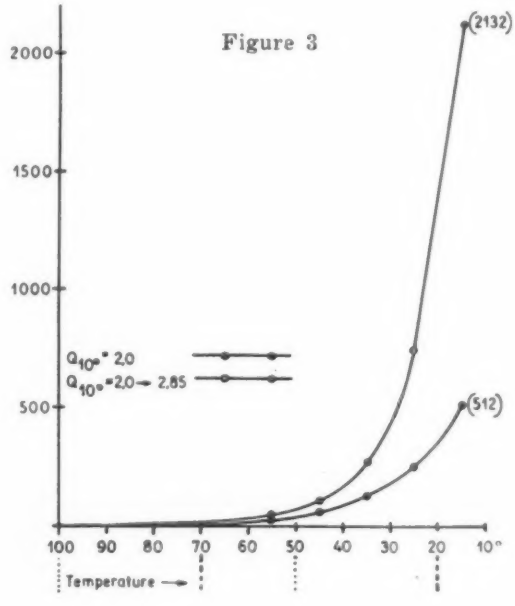
We have talked somewhat at random of monomolecular and bimolecular reactions, or of 1st and 2nd order reactions. However, these designations are not

Figure 2



identical. The former are of a purely chemical significance for simple elementary reactions. But the majority of the reactions in question cannot be considered to be "elementary reactions"; but if the rate of a reaction follows the mathematical expression for a monomolecular or a bimolecular process we term it as a 1st or a 2nd order reaction. Hence in the present case we should use the latter designations.

Figure 3



If the reaction is a 1st order reaction, the rate is directly proportional to the concentration of the initial substance, and we then obtain the well known expression for the specific reaction-rate constant $k = \frac{2.303}{t} \log \frac{a}{a-x}$. On the basis of this expression it then is simple to compute the formula for the period of time involved for 10 percent of the substance to decompose —this then could be the permissible storage period—

$t_{10\%} = \frac{0.104}{k}$ (The same unit of time must of course be used for t and k)

Or, if one is interested in the half life period, which is of interest not only for the radioactive substances but which has been used also for antibiotics, *i.e.*, the period of time until 50 percent of the substance is decomposed:

$$t_{50\%} = \frac{0.693}{k}$$

The latter formula then is exactly the same as that valid for the spontaneous decomposition of radioactive substances:

$$t_{1/2} = \frac{0.693}{\lambda}$$

λ being the so-called disintegration constant.

The figures 4, 5 and 6 represent the course of typical 1st order reactions as given by the relation between the decomposition ("the concentration") and the time, this relation yielding the characteristic bent curve. If instead we chose the relation between the logarithm of the concentration and the time, the resulting curve becomes a straight line.

Thus it appears from the above formulas that the value of the rate constant informs us directly about the stability. Figure 7 indicates the approximate interrelationship between k and the time elapsing until 10 (or 50) percent is decomposed, *i.e.*, the "stability." The time is given with approximation, and the sketch, such as it is, requires the hour to be used as the unit of time. It is my belief that the realization of this interrelationship is of a certain practical importance for pharmaceutical science. It is possible to estimate the stability of a certain preparation on the basis of this figure if the k of the process determining the decomposition of its active ingredient is found in the literature. This is permissible because the reaction involved is a 1st order reaction. In this case the period of time required for a certain percentage of the substance to decompose, *i.e.*, 10 or 50 percent, is the same regardless of the concentration of the substance. However, this is not the case with 2nd order reactions which will be discussed in the following.

Figure 6

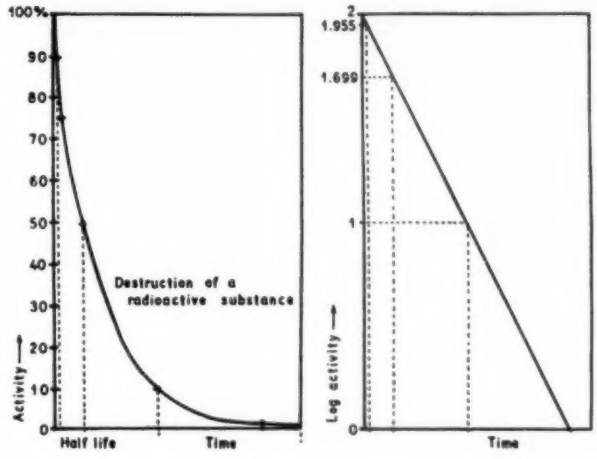


Figure 4

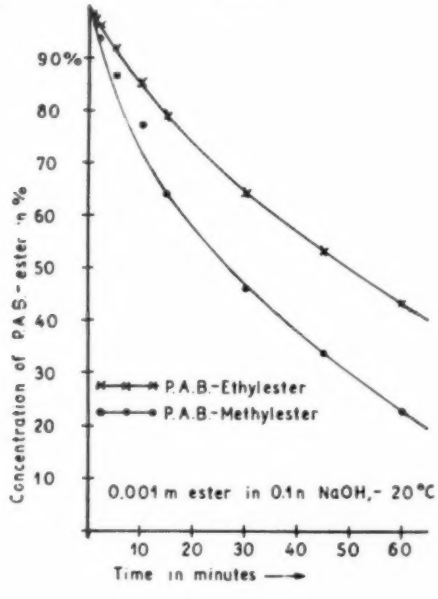


Figure 5

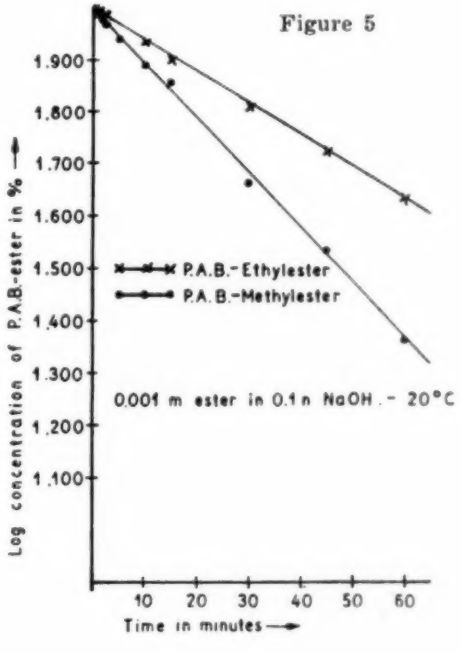
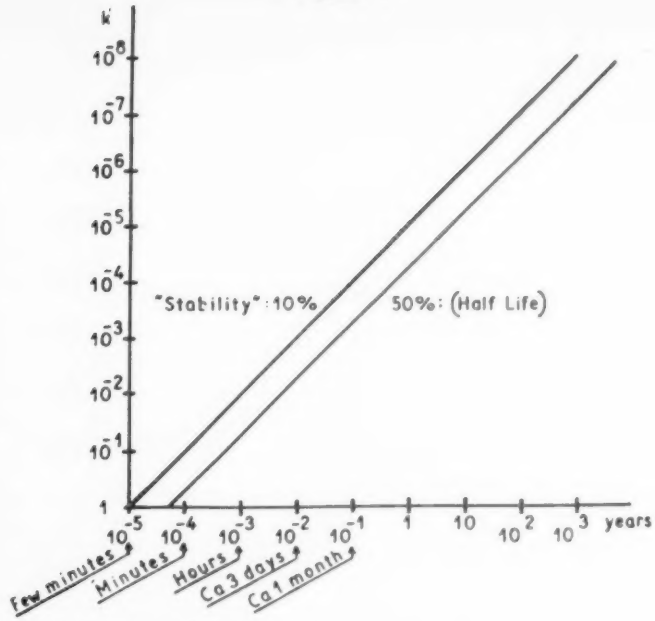


Figure 7



Two Reacting Substances

If we have two reacting substances responsible for the instability of a preparation, the reaction is said to be of the second order. The rate of reaction is in this case dependent of the *molar* concentrations, a and b, of the two substances. A special simple case is if the initial concentrations of a and b are equal, then the rate constant will be expressed by:

$$k = \frac{1}{t} \cdot \frac{x}{a(a-x)}$$

x being the number of moles of the two substances per liter reacting in the time t. The time required for the destruction of a given fraction, 10 percent *e.g.*, is inversely proportional to the initial concentration.

But very often the substances are not present in equivalent amounts. Then a as well as b will be found in the equation, which after the proper mathematical treatment becomes:

$$k = \frac{2.303}{t(a-b)} \log \frac{b(a-x)}{a(b-x)}$$

If t is plotted as abscissa against the $\log \frac{b(a-x)}{a(b-x)}$ we we will get a straight line, the slope of which multiplied by $\frac{2.303}{a-b}$ gives k.

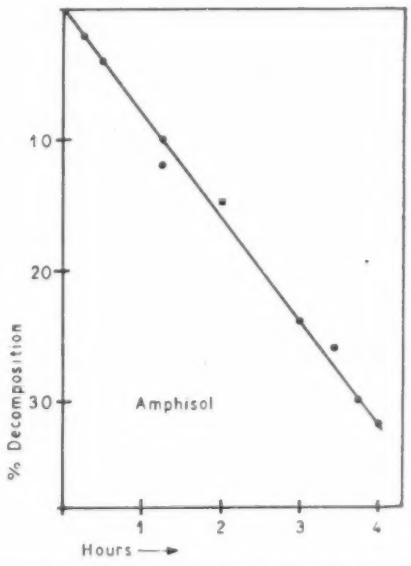
Some of the reactions most important for the stability of pharmaceutical preparations are in fact 2nd order reactions, *e.g.*, the hydrolytic cleavage of the esters. But in general these reactions may be calculated as if they were of the first order. This simple way is possible if one of the reacting substances is present in an excess large enough to be considered to be constant throughout the reaction time. This may be expressed also by saying that we can consider the reaction as one taking place between the ester and the water, which is indeed present in a concentration high enough to be considered constant. This process then is catalyzed by OH^- as well as by H^+ ions. In fact, the equation for 1st order reactions proves to be the tool most used for the processes encountered in pharmaceutical studies.

Reactions of a higher order, *e.g.*, third order reactions, reactions involving three different reacting substances are possibly not of interest at present in connection with the stability investigations in pharmacy, and we will leave them out.

Reactions Independent of Concentration

But processes of *zero-order* must be mentioned. In these reactions the rate is independent of the concentration, some other limiting factors, *e.g.*, surface reactions or absorption of light, being the determining ones. It has been shown only recently that the hydrolytic cleavage of amphisol (amiphenazolum), a rather unstable drug, represents a zero-order reaction. In this case the rate of the decomposition has been shown to be virtually independent of the concentration, and thus concentrated solutions can be considered more stable than dilute.

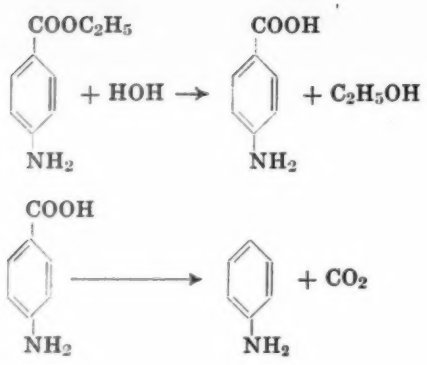
Figure 8



Finally, more complex reactions should be mentioned, *e.g.*, the so-called consecutive reactions which are rather common in the pharmaceutical science. We have a consecutive reaction if the reaction product first formed reacts further to give a second reaction product. This has been found to be the case, *e.g.*, when one of the well known local anesthetics of the benzocaine type is hydrolyzed in acid solution. Then the para-aminobenzoic acid first formed is decarboxylized and aniline is formed (See next page).

This process has been shown to be a reality of pharmaceutical interest. But the theoretical discussion of processes of this type must be postponed to later.

[1] *J. Holt Sörensen,* Dansk. T. Farm. *33,* 61 (1959).



Temperature

We will return for a moment to the question of the temperature coefficient, the Q_{10}^0. As you will understand now, this important factor has been used without the proper criticism in the study and calculation of the stability of pharmaceutical preparations, when experiments performed at a higher temperature have been used to estimate the stability at ordinary temperature. The interval between the two temperatures has often been too big. If this interval is more than 40-50° at the highest it is unavoidable to use the Arrhenius equation in the calculation. If we use this equation in the following form:

$$\log k = \log Z - \frac{E_A}{R \cdot T}$$

k being the velocity constant at the absolute temperature T, Z the number of molecules reacting per unit of time, R the gas constant =4,57 and E_A the energy of activation.

Then this equation represents a straight line, y = log k and $x = \frac{1}{T}$, or in practical graphing $\frac{1}{T} \cdot 10^3$.

E_A is then the slope of the line and log Z the collision number, represented by the part the line cuts off the ordinate. This is the most common way of stating the relation between rate and temperature.

It remains for me to mention the *stabilization, i.e.* the active measures which may be taken in order to increase the stability of pharmaceutical preparations.

But as this point is closely connected with subjects to be discussed in my subsequent lecture I propose to leave its discussion in its entirety to that lecture.

We now return to the two fundamental problems which form the basis for a further discussion, *viz.,*

(1) how to define the concept of the stability of a pharmaceutical preparation, and

(2) which should be the status of the stability and the storage of the preparations in the pharmacopoeia.

A failure to define the concept appears to be out of keeping with the times. The viewpoint of the *United States Pharmacopeia,* correct as it may be from an industrial point of view, is unsatisfactory for the pharmaceutical practice as a whole.

The standpoint of the *British Pharmacopoeia, viz.,* to state the period for which a certain preparation "may be expected to retain its potency" is excellent inasmuch as according to its wording it provides certain information—instruction, in fact. For the person unable to judge, or not wanting to judge, the potency of the preparation, this specification provides a definite statement of the period of stability.

In a way, the view point of the *Danish Pharmacopoeia* is the one affording the fewest reasons for doubt. Here definite stability periods are given for a large number of preparations. Although the basis of these specifications might have been more unequivocal we are now in a position to pronounce them to have stood their test in practice, on the whole.

In my opinion, we would do well to adopt either the British or the Danish point of view in this respect, and in actual fact they are very similar. But whichever one we choose to adopt, it is necessary to further build up the system. Personally, I should like to recommend the following definition as a guidance for further work in this field:

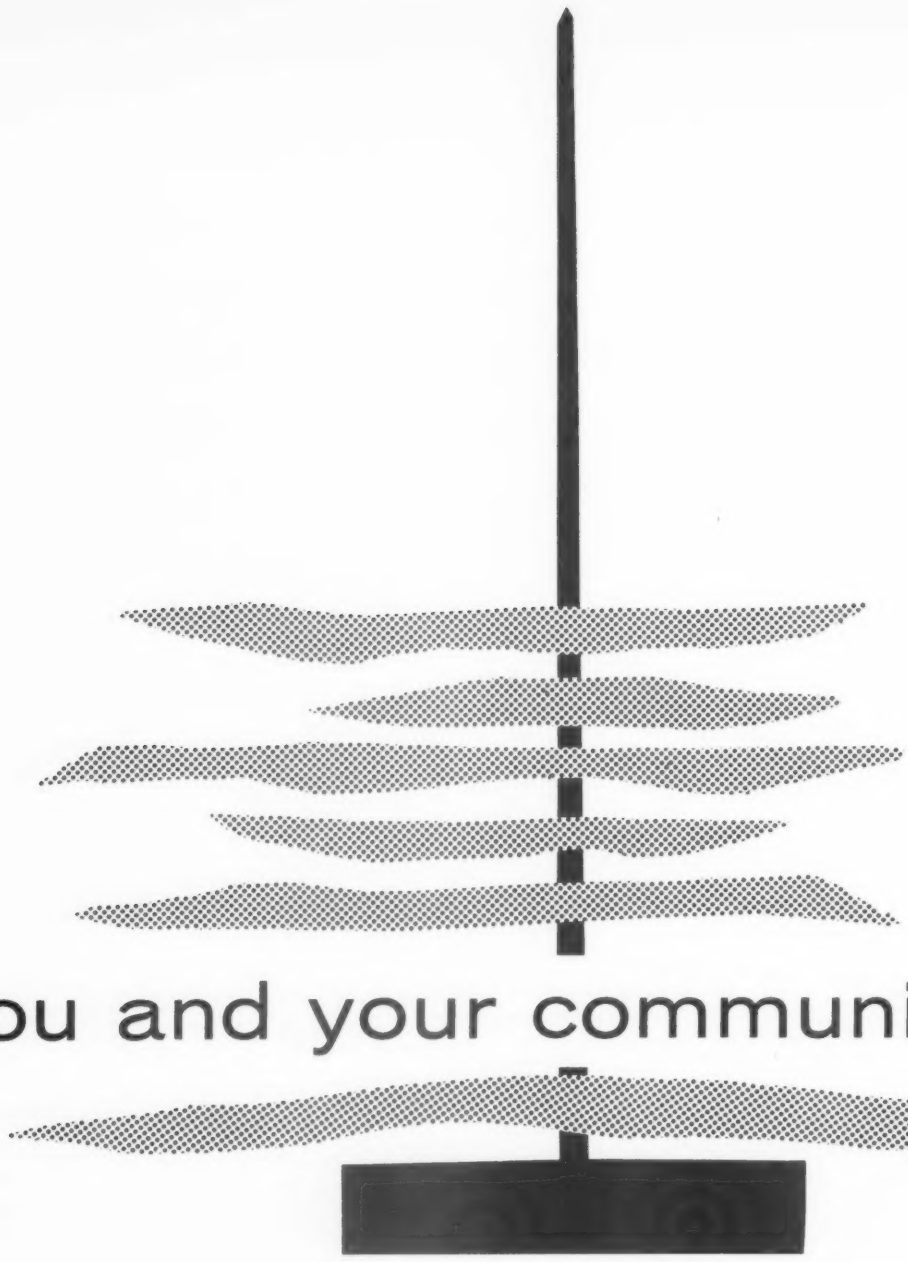
The stability of a pharmaceutical preparation is the period of time from the completion of the preparation and until it no longer fulfills the specifications made in the pharmacopoeia, or until the potency has been reduced by not more than 10 percent.

This definition has the advantage of leaving open the question of a specific period of stability for the individual preparation, and in addition it is possible to state a limit other than the original 10 percent. In a way this definition is a composite of the individual standpoints of the British and the Danish pharmacopoeias.

This formulation allows for a further projection of the problem, a further specification of the stability of each individual preparation, enabling us to reach the ultimate goal. This must be that the permissible storage period for each preparation which has been adopted by or which is to be adopted by the pharmacopoeias or by other more or less official collections of prescriptions should be stated to be limited to a definite time, a definite reduction of its potency, or both, and this is possible within the limits of the above formulation.

In any case, we owe a debt of further work on the stability problem to our profession. Anybody introducing a new preparation into the market, or anybody composing a prescription for a new preparation, should be in honor bound to provide specific information concerning the stability of that preparation.

In connection with the view which it has been my privilege to air here today I should like to conclude with the statement that I am firmly convinced that *apart from all other limits a maximum storage period of 5 years should be the ultimate requirements for all pharmaceutical preparations.*



you and your communications

by E. Burns Geiger

► IN TALKING TO YOU FELLOW HOSPITAL PHARMACISTS about communications, I am reminded of an incident that was supposed to have happened in the Bureau of Standards several years ago while I was working with your new president in Washington. A plumber wrote the government to find out if hydrochloric acid could be used to clean plugged pipes.

A bureau scientist replied: "The uncertain reaction processes of hydrochloric acid place pipes in jeopardy when alkalinity is involved. The efficacy of this solution is indisputable, but the corrosive residue is incompatible with metallic permanence."

The plumber wrote back thanking the department for its quick approval for the use of the acid. Somewhat dismayed, the scientist wrote another letter to the plumber.

"Hydrochloric acid generates a toxic and noxious residue which will produce submuriate invalidating reactions. Consequently, some alternative procedure is preferable."

Once more the plumber mailed a letter to the scientist thanking him for his fast action in confirming the use of hydrochloric acid. There was only one thing for the desperate scientist to do. That very hour,

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Presented at the Annual Convention of the American Society of Hospital Pharmacists, Cincinnati, Ohio, August 17, 1959.

he sent the plumber this telegram: "Don't use hydrochloric acid. It eats hell out of pipes."

Ladies and gentlemen, let's be candid. How often do *you* receive business letters, hospital memos, or notes that make you think: "Someone's crazy, I can't make heads or tails of this stuff." Then you try to re-read the correspondence but you find only business jargon, clichés, double-talk, and gobbledegook.

Well, I receive that kind of letter all the time and so, probably, does everyone in this room. And when I do, I feel a special kinship with the business executive who sends memos saying "Good-grief-why-don't - you - people - learn - to - use - plain - English - around-here?"

Now there are two ways to avoid being on the receiving end of a "good grief" memo. One simple solution is never to write another word. From that moment on, no one will ever criticize you for the use of slang, bad syntax or a split infinitive. But there are some obvious drawbacks—you no longer can communicate with anyone out of earshot, you become somewhat isolated, and your ability to contribute your service declines. The other solution is to learn to present your thoughts with greater clarity. I would like to discuss with you this afternoon various ways this can be done.

English Usage

About nine years ago, the editors of *Fortune* magazine published some articles on English usage and the field of communications and they found that the American businessman fumbles and mangles the written word. Many solutions were offered but perhaps the best one was voiced by a top management consultant. He said it was "high time the American businessman discovered the English language—it would be useful to him." This need has never been so urgent.

In private conversations, many people are concise, interesting, and persuasive. They never use such words as "finalize" or "interdepartmental coherence." But once they start to write, they sound lifeless, stuffy, and ambiguous. Indeed, they not only use words that most people don't understand, but in the process, they waste time and countless dollars as well.

However, this is not a problem that is peculiar to businessmen—it affects every segment of our population. Wherever there are people, there is a need for some kind of communication and a great deal of it is written—TV scripts, plays, business letters, office memos, records, and vacation post cards. And when communication between people breaks down, progress begins to flounder, TV sets are turned off, and people begin to doze in the third row.

That exchange of letters between the plumber and the scientist is not as far-fetched as it may appear. Correspondence specialist Richard Morris estimates that roughly 15 percent of all letters—about one out of every seven—need never have been written if all preceding correspondence had been in "regular English."

Consider for a moment how much time and effort could be saved if all excess words were cut from your weekly stack of business letters, hospital memorandums, and mail. *Fortune* magazine estimates that a business firm that sends out one million letters a year could save up to $200,000 in labor, mailing, and paper costs, if everyone would learn to write clearer, shorter letters.

True enough, you hospital pharmacists don't write a million letters a year—not each one of you at least—but you do compose plenty of memos, letters, and notes and many of you keep the records for your hospital pharmacy and therapeutics committees. Therefore, any reduction in your correspondence and paper work would help cut costs and—even more important—it would help you get your ideas across better.

How well you express your ideas is important, perhaps more important than you realize. Hospital pharmacists and other professional people spend as much as half their time every day trying to persuade others to adopt new ideas, services, or products. While some of this communicating is by the written word, the bulk of it is in person-to-person contacts.

Four Step Method for Writing

Unfortunately, there is no magic formula that will give everyone the power to persuade, but there are some techniques that will help you better organize your thoughts and marshal your facts and figures. One of these methods, which can be broken down into four steps, was designed for writing memos and other correspondence, but it can be used with telling effect in speeches or even in private conversations.

With this method, you begin by describing the benefits the other person is to receive from your proposal. Number two, you describe your proposal and tie it with the benefits. Number three, you tell how your proposal works and how it will provide the benefits you have already promised. In the last step, you summarize the first three points and then make a call for positive action.

Let me give an example to show you how this four-step method works. Let us suppose that your overwhelming desire in life is to bring pay TV into every American home. Perhaps you and I don't think this is a very practical proposal, but for the moment, let us use it to illustrate how we should go about winning friends and influencing people in support of our cause.

Whether we are giving a speech or writing a letter, we would begin in the same way. Step number one.

Tell the benefits of your proposal. In this case, we would say, "What Americans need is more enjoyment and relaxation and an end to worries and tension."

I suppose reasonable people would agree that these are fairly worthwhile objectives. Then comes step number two. We tell people what our proposal is and how it is tied in with these benefits. Perhaps here we would say, "The way to get better entertainment is through pay TV. By installing this system, Americans would automatically get improved TV shows and more educational programs. Through education, we would learn to relax our tensions and many of our worries would disappear."

Then we would explain that through pay TV, old Joan Crawford movies would be replaced by new Joan Crawford movies. Instead of low budget Westerns, panel shows, and situation comedies, there would be *big* budget Westerns, panel shows, and situation comedies.

Then comes step number three. We must explain how our proposal works. In this case, we would tell our audience that to enjoy outstanding entertainment all they would have to do is drop a few quarters into their TV sets each night. If they didn't like that method, they could pay for their TV shows at the end of the month along with their electric and gas bills.

With the last step, we summarize the first three points and then make our call for action—we ask our audience for support. In this case, we would tell them to write their local congressman, TV set manufacturers, or advertisers. To write someone anyway.

This method for friendly persuasion is suitable not only for pay TV arguments, but all other situations—anything from trying to round up supporters for Fair Trade legislation to winning support for building a parking lot across the street from your hospital. If you are able to organize your thoughts in this way, you may also be able to improve your daily relations with patients, doctors, hospital administrators, your own pharmacy staff and your family and friends.

Once more, here are the four steps: one, describe the benefits of your proposal; two, describe your proposal and tie it in with the benefits; three, tell how your proposal would work; and four, summarize the first three points and then make a call for positive action.

You will note that politicians use this same strategy in their campaign speeches. First they tell their constituents the various benefits needed by the people—old age pensions, lower taxes, stopping recessions, curbing inflation, and peace and prosperity.

Then they tell what their party platform stands for and, sure enough, each party believes in all these same benefits. Next the politicians explain how their new proposals will work—although sometimes the new taxes are not mentioned. Finally there is a summary, and then at the very end, you will notice, there is always the call for positive action—in this case, votes. During the past twenty years, politicians have changed and so have their speeches and their appeals. But the way politicians present their arguments remains basically the same.

Basic Qualities of Writing

After we know how to organize our thoughts, we are ready to choose our words and sentences—and that requires great care and discipline. In order to write so others will understand us, we must keep in mind five basic qualities of successful writing: clarity, conciseness, correctness, courtesy, and character.

The first one, clarity, is the basis of communications. To be sure that people understand you, use specific, concrete language. For example, instead of saying "developments in the hospital are interesting," tell what happened: a new wing was added, the staff was enlarged, everyone got a raise.

In writing, use words that are specific, not general; definite, not vague; concrete, not abstract. Moreover, let the tone of your writing be positive, not negative. When the meaning of a long sentence is not clear, re-write it, and if necessary, break the sentence up into two or more shorter ones. But don't break up sentences if you don't have to.

The second quality is conciseness. Omit needless words. As an English professor once wrote: "A sentence should contain no unnecessary words, a paragraph no unnecessary sentences, for the same reason that a drawing should have no unnecessary lines and a machine no unnecessary parts. This requires not that the writer make all his sentences short or that he avoid all detail and treat his subjects only in outline," but instead make every word count.

The third basic quality is correctness—good English usage. Obviously, no one plans to say "ain't" or "we is" in a memo to doctors or the hospital administrator. But what concerns many people is the mutilation of the English language with jargon, the overuse of advertising lingo, and goobledegook. When you are writing, try to keep intact the form, variety, and richness of the English language. If you err, let it be on the side of established usage. There is a place for occasional off-beat expressions and slang, but use them sparingly; otherwise, they will quickly lose their freshness and vitality. If anyone should doubt this, let him re-read the Declaration of Independence or the Gettysburg Address, and see if these documents could be improved by slang or the "technical verbiage of business communication-type exchanges."

The fourth quality, courtesy, must come naturally; it can not be forced. Remember, only courtesy heals

the wounds of misunderstanding and disagreements; bluntness or rudeness never will. What is often written in haste without any thought given to the other fellow is quickly regretted and slowly forgotten.

The fifth basic quality is character. Your writing must reflect you and your personality, but therein lies one of the great pitfalls. Never distract your reader from the substance of your thoughts by injecting too much of your mood and temper into your writing. If you write clearly and concisely, your personality will inevitably be revealed to others; that is sufficient. Leave well enough alone.

Use Established Forms

Now with the rules and methods I just gave you in mind, let us look at some correspondence. As hospital pharmacists, you know that letters, office memos, and records must take a definite form if they are to receive the attention they deserve. Let that be your guide—always use the established forms of correspondence.

In writing business correspondence, there are three basic characteristics that you should strive for: unity, coherence, and emphasis. How successful you are in achieving these characteristics will determine how well you can write.

Psychologists say that the human mind learns only one idea at a time and that's why you must strive to unify your thoughts. After you have unified your ideas, you must present them in a logical order to lend coherence to what you have to say. To do this, use the four-step method of persuasion and the five C's: clarity, conciseness, correctness, courtesy, and character.

Finally allot the greatest space and emphasis to your most important idea and give it the most prominent position, either at the beginning or at the very end of your letter or memo.

Now let us see how these rules can be applied to correspondence. Let me give you an example. Here's a memorandum written by a pharmacist to a hospital administrator concerning a universal problem in hospitals today. In the memo, the pharmacist uses our rules and methods to persuade the hospital administrator to give his pharmacy more space.

Here's the memorandum.

MEMORANDUM

TO: Immediate Superior (Administrator, Asst. Administrator, Chief of Medicine, Other)

FROM: Chief Pharmacist

RE: Improved Efficiency of Pharmacy Operation

ESTABLISH MENTAL ACCORD

Increased savings, added service, improved quality of medical care, and saving time for hospital personnel are our objectives for operating the hospital.

TIE IN YOUR OBJECTIVE

A careful analysis of our current operation and physical facilities has shown that substantial gains toward these objectives can be made in the pharmacy.

This study has shown that by making a small addition to the existing pharmacy, significant progress can be made toward these objectives.

When the pharmacy is expanded, we will achieve:

SHOW PROOF

1. *Increased Savings*

   – by an expanded manufacturing program for producing standard formulae in quantity, special formula requests from the various services, laundry and housekeeping products and stains for the laboratory.

   – by quantity and volume purchase discounts, and

   – by a more efficient and orderly schedule without requiring additional personnel.

2. *Added Service*

   – by handling, more efficiently, the needs of the patients and the staff.

3. *Improved Quality of Medical Care*

   – by manufacturing the special formulae required by our medical staff, preparing bulk products and maintaining sufficient inventory.

   – by faster and more efficient methods of operation.

4. *Saving Time for Hospital Personnel*

   – by filling and distributing all floor baskets at the same time instead of using the cumbersome stagger system.

   – by more effective dispensing of narcotics.

These gains can be achieved at a very small cost to the hospital by converting Room B, which is adjacent to the southern end of the Pharmacy into the added area. This room is now used for storage by our Purchasing Agent with whom this plan was discussed. He will rearrange the shelves in his main storage room which will free the ten-foot square area of Room B.

With gas, water and electric lines currently installed in Room B, the removal of the non-supporting, separating wall will make this area a continuous part of the Pharmacy proper at a modest cost to the hospital. This will then place the attainment of our objectives within reach.

ASK FOR ACTION

Your early consideration and approval of this proposal will be appreciated.

Chief Pharmacist

cc: Purchasing Agent

Your Ears Are Your Best Asset

I have saved for the very end the most important fact about present-day communications: in dealing with people, your ears are your best assets.

The best way to win friends and influence people nowadays is to listen to them. Recently a professor of applied psychology from a large Eastern university wrote that the "biggest block to effective personal communication is man's inability to listen intelligently, understandingly, and successfully to another person."

Sociologists have found that listening to the other fellow may in itself be far more persuasive than anything we have to say—if it is done with an honest interest and not an attitude of let-the-guy-talk-himself-dry-and-maybe-he'll-go-away.

Considering how important listening is, let me suggest that you give people all the attention you can bear. By listening, you are bound to learn something of value sooner or later and this new knowledge may be of great use to you in the years to come.

If you can't bear to listen to anyone—beware, for people will soon stop listening to you. Remember what Dostoyevsky said in "The Brothers Karamazov," "If the people around you are spiteful and callous, and will not hear you, fall down before them and beg forgiveness; for in truth you are to blame for their not wanting to hear you."

It's the same way with unanswered letters and memos. How many have you sent out that have never been answered? Who is really at fault for their not being answered? Reflect on this and in the coming months, if you think your letters and memos might be partly to blame, may I suggest that you browse through the little booklet "Put It In Writing" that will be distributed to you later on this afternoon. I think it will be helpful to you.

Moreover, though you may never get a letter from a plumber asking how to use hydrochloric acid to clear plugged pipes, you do get questions all the time about this-or-that new drug. I'm sure you know the answers. Just put it in writing with clarity, conciseness, correctness, courtesy, and character.

If you do, people will always know what you mean.

THE BETH HOLIM FORMULARY OF LONDON (1749)

by ALEX BERMAN

► In 1749, there appeared in London an 89-page Latin formulary entitled *Pharmacopoeia contracta; in usum nosocomii ad pauperes e gente lusitanica curandos nuper instituti, a J. de C. S. et P. de L., M.D. et ejusdem nosocomii medicis concinnata* ("A concise pharmacopoeia; for the use of the hospital recently founded for curing the poor of the Portuguese community. Compiled by J. de C. S. and P. de L. M.D. and physicians of the same hospital"). The hospital referred to was the *Beth Holim* ("House for the sick") which had been formally opened in 1748 by the Spanish and Portuguese Jewish community in London.

The *Beth Holim* formulary is now exceedingly rare. Fortunately, this writer was able to consult one of the few existing copies at the Bibliothèque Nationale in Paris.[1] Two prominent bibliographers, Scherer and Callisen, have erroneously listed this work as intended for a hospital in Portugal rather than for an institution in London.[2] Confusion has also been engendered in the literature by references to the hospital as the "Portuguese Hospital" of London instead of the official name, *Beth Holim*.

About two decades after its founding, the *Beth Holim* admitted an average of 120 patients per year.

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"The Jerusalem Infirmary," a scurrilous attack against the Beth Holim in an anonymous engraving which was published in 1749. Note the title page of the Beth Holim formulary hanging on the left wall over the apothecary's room. (From Alfred Rubens' Anglo-Jewis Portraits, London, 1935)

Jacob de Castro Sarmento (1692-1762), co-author of the Beth Holim formulary. Portrait by Pine, engraved by Houston. (Courtesy of the National Library of Medicine, Washington, D.C.).

PHARMACOPOEIA

CONTRACTA;

IN USUM

NOSOCOMII

AD

Pauperes e gente *LUSITANICA* curandos nuper inſtituti.

A *J. de C. S.* & *P. de L.* M.D. et ejuſdem Nosocomii Medicis concinnata.

Medicamentis multum antiqui Auctores tribuerunt, horum autem uſum ex magna parte Aſclepiades non ſine cauſa ſuſtulit.

Verum multa admodum corporibus noſtris incidere conſueverunt, quæ ſine medicamentis ad ſanitatem pervenire non poſſunt.

Celſ. præf. ad Lib. V.

LONDINI:

M.DCC.XLIX.

Title page of the Beth Holim formulary. (Courtesy of the Bibliotheque Nationale, Paris)

Hospitalization, medicine, and medical advice were supplied gratis to the sick-poor of the Sephardic Synagogue. For example, during the period 1753-1754, some 2,318 prescriptions were filled by the hospital's apothecary.[3] The *Beth Holim* was also one of the earliest London hospitals to provide special wards for women in child-birth.[4]

The Authors

Two Portuguese Jewish physicians, both of whom were among the founders of the hospital, were the authors of the *Beth Holim* formulary.

The senior author, Jacob de Castro Sarmento[5] (1692-1762), born in Portugal, received doctorates in medicine from the Universities of Coimbra (1717) and later Aberdeen (1739); he was admitted a Licentiate of the Royal College of Physicians (1725) and became a Fellow of the Royal Society (1729). A scholar of repute and a prolific writer, Castro Sarmento's interests were reflected in his publications on philosophy, natural science, medicine, and Hebrew theology.

Philip de la Cour[6] (d. 1786) was born in Portugal as Abraham Gomez Ergas. He obtained his medical degree at Leyden (1733)[7] and subsequently came to England where he established a fashionable practice in London and Bath. In 1751, he was admitted a Licentiate of the Royal College of Physicians[8], and in 1783 was apparently practicing in London, since his name is listed in the *Medical Register* for that year.[9] Three years later, Philip de la Cour is known to have died in poverty in Amsterdam.

Evaluation of the Beth Holim Formulary

The work of Castro Sarmento and de la Cour appears to have been the first official formulary printed for an English hospital.[10] It was preceded in Great Britain by the formulary of the Royal Hospital in Edinburgh (1746). Only much later in the 18th century did other English hospitals follow suit.[11]

Of the 238 formulae in the *Beth Holim* publication, 23 were included in William Lewis's *New Dispensatory* (1753), and 83 formulae found their way into the second English and Latin editions of the *Modern Practice of the London Hospitals* (1770).

Professor Urdang, in his excellent commentary on the *Lititz Pharmacopoeia,* concluded that "obvious analogies" could be seen between five of the formulae in the *Lititz Pharmacopoeia* and five of the 23 *Beth Holim* medications listed in Lewis's New Dispensatory.[12] A comparison of the Lititz work with the original *Beth Holim* formulary reveals that additional analogies can be found.[13]

There is no doubt that the two Portuguese physicians had produced one of the finest hospital formularies of that time with respect to organization, succinctness, and choice of medication. This is apparent when one compares the *Beth Holim* formulary with the earlier works of Henry Banyer and Robert Poole, or with the first printed formulary of the Hôtel-Dieu in Paris, published in 1753.[14] The comparative study of early English hospital formularies (1718-1800) now being made by this writer will focus more sharply on the place of the *Beth Holim* publication in the mainstream of 18th-century English hospital formularies.

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8. Munk, *op. cit.,* vol. 2, p. 155.

9. *The Medical Register,* London, 1783. Printed for Joseph Johnson, No. 27, St. Paul's Church Yard. The copy consulted was in the Wellcome Historical Medical Library, London.

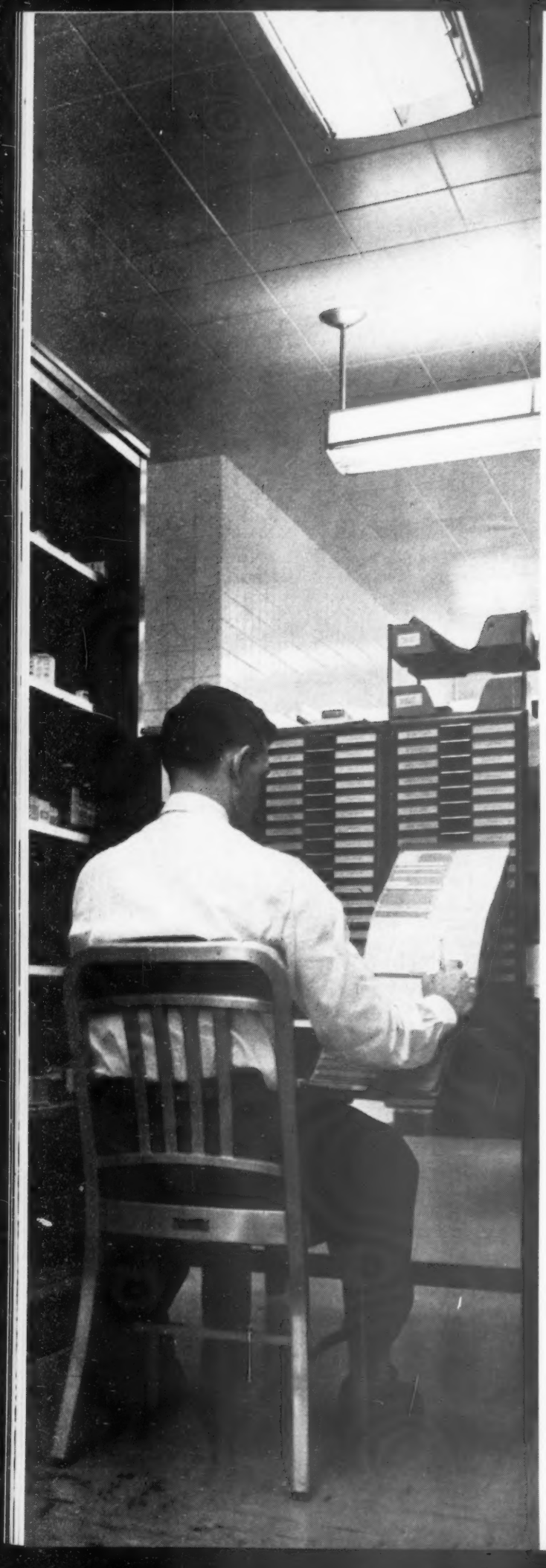
10. The *Pharmacopoeia Pauperum* of Henry Banyer which had appeared in four editions from 1718 to 1739, and the *Physical Vade Mecum or Fifth Gift* of Robert Poole which had been published in 1741, had listed the medications of some of the London hospitals, but these works were not official in the sense of having been published specifically for or by a hospital.

11. The first official and separately printed formulary to appear in England after the *Beth Holim* publication was that of St. George's Hospital in 1768 (*Pharmacopoeia in usum nosocomii londoninensis Sancti-Georgi Londini, excudebat Hughs*). This was followed by St. Thomas's (1772), Bristol 1777), Guy's (1782) and St. Bartholomew's (1799).

12. Urdang, George: "Addenda to the Lititz Pharmacopeia" in Edward Kremer's *Documents pertaining to the medicinal supplies within the North American colonies from 1643 to 1780.* American Institute of the History of Pharmacy. Madison, Wisconsin, 1944, p. 13.

13. For example, compare respectively the following of the *Beth Holim* publication: Myrrh Pills with Iron (p. 60), Infusion of Serpentaria with Vinegar (p. 45), Yellow Basilicon with Red Precipitate (p. 87), with the following formulae in the *Lititz Pharmacopoeia* (1778 edition): Chalybeate Pills (p. 18), Infusion of Serpentaria (p. 14), and Red Precipitate Ointment (p. 31).

14. *Formules médicinales de l'Hostel-Dieu de Paris,* Paris 1753. See *Bull. Amer. Soc. Hosp. Phar.,* 13: (May-June) 218-219, 1956.



A PILOT STUDY OF DRUG CHARGES IN COLORADO HOSPITALS

by HUGH F. KABAT
and F. C. HAMMERNESS

► DRUG PRICES IN GENERAL AND HOSPITAL DRUG PRICES in particular have been the subject of criticism by both the lay and professional press. Both groups have felt that in most instances the prices charged for drugs in hospitals were too high. If the prices charged for

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Hospitals collect much information necessary to analyze their financial operation but more should make use of it. We must strive to be more realistic in costing and use better planned pricing methods in charging for all services

drugs are not equitable to both the public and the institution then the criticism is justified.

Purpose of Study

The purpose of this study was two-fold: first, to determine whether prices charged for drugs in a selected sample of Colorado hospitals were fair and equitable; and secondly, the validity of the information obtained for use in determining the actual cost of dispensing drugs in a hospital. Only by knowing the actual cost can the hospital price drugs in such a manner that the hospital recovers its costs and at the same time makes these drugs available to the patient at the lowest cost possible.

The results presented in this study are from a survey of prices charged in a selected sample of Colorado non-profit hospitals representing 34 percent of the hospital beds in Colorado where individual charges were made for drugs. Each hospital was asked to price a list of 40 pharmaceuticals currently being used in this area. The prices obtained were statistically compared with the costs involved in the dispensing of these pharmaceuticals in an effort to determine whether or not the prices charged were significantly higher or lower than the total or actual costs incurred by the pharmacy.

Methodology

The cost of each prescription included the cost of ingredient (s), label, container, labor and overhead and was considered to be the break-even point above which a profit was made and below which a loss was incurred. Ingredient costs were obtained from the 1959 *Drug Topics Red Book*. The cost of labor was determined by multiplying the average salary received by pharmacists in this area by the time required for dispensing. The norms used for the average time required to fill the prescription were taken from *Standard Prescription Dispensing-Compounding Time Norm Tables* by S. B. Jeffries. The cost of overhead was available from only two of the hospitals surveyed. It was reported as 65 cents per prescription in a large hospital dispensing 152,000 prescriptions per year and 68 cents in a small hospital dispensing 9,500 prescriptions per year. The figure of 65 cents per prescription was used in this study. Overhead is a reflection of the total services offered by the hospital. An interesting observation in these two dissimilar hospitals was the small difference in the overhead per prescription of three cents. It would appear that those efficiencies that were achieved in larger hospitals were eaten up by the increase in services that were offered.

Conclusions

Admittedly the results of this study are incomplete and much further work needs to be done. The following conclusions are based on the information obtained during this study:

1. Hospitals do collect much of the information necessary to analyze their financial operations. However, fuller use of this information should be made. Departmentalizing of expenses and allocation of costs would be useful in a more complete cost analysis.

2. In the sample of pharmaceuticals priced, 59 percent of the drugs were dispensed at a dollars and cents loss. Another 10 percent yielded less than 26 cents per prescription above break-even costs.

3. Prices in three of the hospitals were significantly higher and in one were significantly lower statistically, at the 5 percent level of confidence, than the costs of dispensing in this sample of 10 hospitals. This means that the results obtained could have occurred by chance only 5 times out of 100.

4. Some of the items exceeded their break-even cost by handsome margins. Seventeen percent of the prescriptions had a net profit on sales of more than $1.00. They were primarily the more expensive medications. These drugs, relatively few in number, not only made up for the loss on the other drugs, but also placed the pharmacy in a favorable profit position.

5. Another factor which inflated the hospital pharmacies' profit picture was that the cost of syringes and needles was not charged to the pharmacy department as an expense. Yet pharmacy was expected to recover these costs with their medication charges. Behavior such as this inflates the profit picture and makes pharmacy charges subject to criticism.

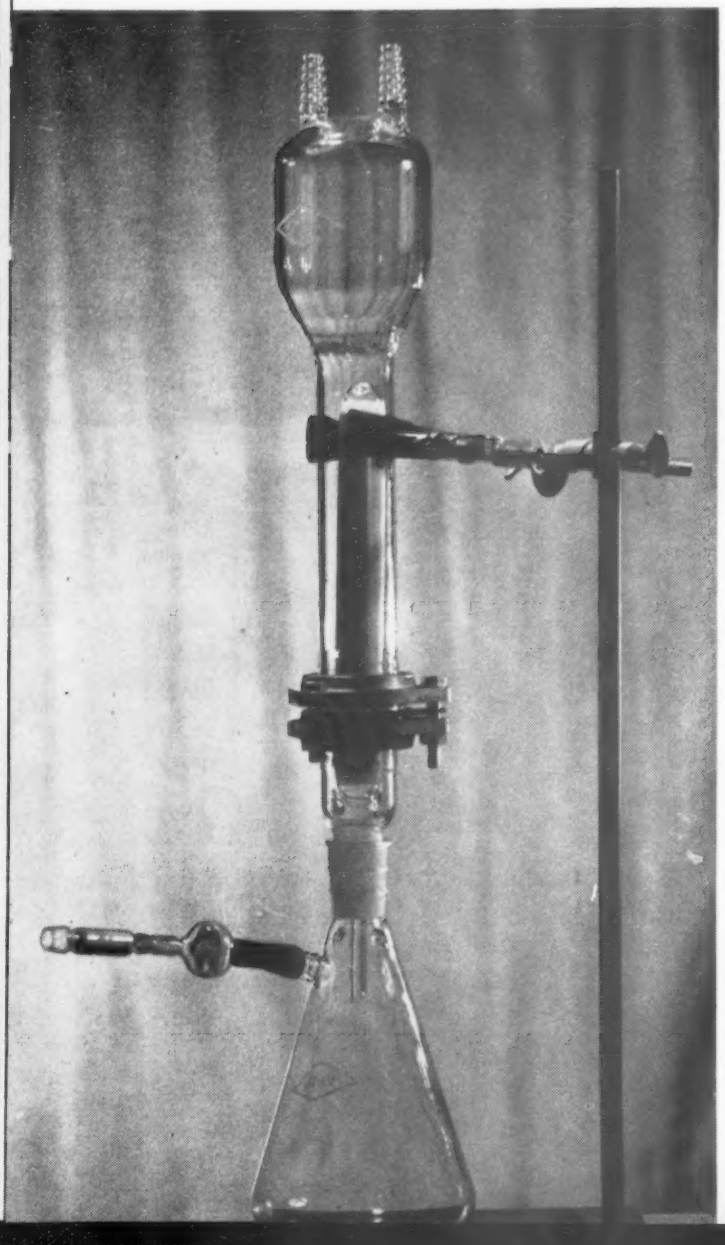
6. Hospitals must strive to achieve professional economic security through more realistic costing and better planned pricing of all hospital services.

PREPARATION OF

SKIN BANK FLUIDS

by OTMAR M. NETZER

Bacterial Filtration Assembly



► SKIN GRAFTING IS PERFORMED FOR THE PURPOSE of closing certain body defects. The history of free tissue grafting goes back for ages, but its scientific origin dates from the second half of the nineteenth century. Through his success in an epidermal grafting in 1869 and his publications in 1872 on his experiences in more than fifty cases, Revardin led the interest of the medical profession towards the possibility of free transplantations. However, the real development of skin grafting started only after the end of the First World War, improving considerably during and after World War II.

Revardin transplanted small pieces, "islands," of epidermis called "pinch grafts" ("greffes epidermiques). Ollier (1872) recommended the use of large pieces of partial thickness of skin covering the defective surface "*in toto*," and Thiersch (1886) improved on this method. Wolfe (1875) and Krause (1893) reported transplantations of the entire thickness of skin. Others, as T. S. Davis (1914) introduced variations on these methods. Today the two most widely used grafts are the large split graft, consisting of the partial thickness of the skin, and the large full thickness graft. The first one is used on granulating surfaces as well as on "clean areas," the latter can be employed only if the host area is "clean."

Types of Transplantations

There are three types of transplantations, classified according to the donors. The transplant may be obtained from the very same person (autogenous), from another person (homogenous), or from a different species altogether (heterogenous). So far the greatest chances of regeneration and survival of a graft present themselves in autogenous transplantations. Homogenous grafts do not seem to take permanently in warm blooded species, except for identical twins and for individuals with an alpha-gamma-globulinemia. The usual persistence of homografts in human beings is from three to twelve weeks, sometimes up to eleven months. However, it is hoped that some method may be developed which will permit permanent homografts and thus surmount one of the greatest obstacles.

Free transplantations are employed in corrections of scars and in closing operative wounds, both instances usually allowing previous preparation. In cases of accidental wounds, in the treatment of war injuries and burns, the grafts serve as a life-saving, emergency

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and biologic dressing to tide the patient over a critical period. Burns grafted without leaving open wounds or irritated contractures do not develop carcinoma, the possibility of bacterial infections is limited, a decrease in pain is observed, the period of morbidity and hospitalization is considerably shortened and the rehabilitation of the patient is more complete. In addition, valuable material such as plasma, albumin, whole blood, sterile electrolyte solutions, antibiotics, morphine, anesthetics, dressing etc. is saved. This may be of the greatest importance especially in any kind of disaster.

Depending on the extent of the injured or burned area and the condition of the patient, autografting or homografting may be administered after suitable initial treatment. However, in more severe cases where a longer operation seems dangerous an autogenous transplantation would place an additional load on the patient. Therefore, homografts are employed in those cases. The homografts are to be used fresh or as preserved postmortem grafts. The latter are quite preferable, as they provide a large amount of grafting material from a single source without disfiguring the donor. Futhermore, this method avoids discomfort, pain and loss of time involved for the eventual live donors and represents considerable saving in operative time, postoperative care and all the material previously mentioned. This may be illustrated by a recent report in one of the Eastern newspapers on the use of 100 live homograft - donors to graft one single burned patient, or by the case of a patient with large open burnscars on his legs who had been in bed for 17 months and had purchased $1,700 worth of a preparation recommended for burns plus expensive dressings and hospital care. The burned area in this case was repaired by autografts which survived and the patient was completely rehabilitated. All this was accomplished in just one single operation.

Postmortem homografts may be transplanted directly like autografts, or they may be stored for a certain length of time. In 1912, Alexis Carrel created the basis for our modern methods of preservation of the skin. Most of the subsequent clinical work recorded in literature is concerned with the storage of skin for homografts. Coller (1925) reported preservation of autografts for six hours after their removal. A longer storage of skin for autografts was clinically reported in 1945, but its practical use did not widely increase. Since then, different methods of storing skin in viable or nonviable state were developed and improved. The storage center of these grafts is called a "Skin Bank." A number of skin banks, on larger or smaller scale, are already established. For example, the Tissue Bank of the National Naval Medical Center at Bethesda was founded in 1950 and handles skin and other tissue material such as facia, dura, cartilage, bones and blood vessels.

As previously mentioned, there are different methods of preserving and storing skin some of which are the following.

Postmortem homografts frozen at -72°C. and dried by the lyophilizing process are storable and remain stable for a long time at room temperature; they are easily transported and prepared for use by the addition of sterile saline 30 minutes before use. However, the skin so treated is nonviable and seems to disappear earlier than homografts stored in balanced salt solution.

Another method of skin banking is the preservation of homografts at low temperature with or without employment of glycerol in the procedure. Thus it may be possible to store skin for a longer period of time with the aid of glycerol at -79°C. and to thaw it later in sterile Ringer's solution with the majority of the cells still surviving.

The storage of skin at 3° to 5°C. in saline-antibiotic solutions with or without added nutrient media is another possibility. Skin so stored is viable for approximately three weeks. Grafts not used during this time may still be processed and stored at low temperatures or lyophilized and kept at room temperature. This method has several advantages. It is the easiest and simplest method of skin banking, the time, material and equipment required are minimal and the grafts are always ready for immediate use. For the present, a skin homograft bank of this type—like some of the other clinical banks, *e. g.* the blood bank—cannot be established without some waste. However, such cutaneous material not used for grafting can be employed for tissue culture studies and other research work so that each jar of skin may lead a little step further toward the development of the ideal method of storing skin. Until this goal of viable skin preservation is reached, the above mentioned kind of banking will be found mainly in larger hospitals and in those receiving the greatest number of emergency cases from any community.

Formulas and Preparation

The formula and procedure of preparation of a balanced salt solution containing plasma and an antibiotic, the Skin Bank Fluid, are given below. It is the preservation medium prepared by the University of Michigan Hospital Pharmacy Laboratory and used at the University of Michigan Hospital Skin Bank for storage of skin autografts as well as skin homografts. This form of storage of cutaneous material is adaptable to hospitals of all sizes and, in particular, to those hospitals where the pharmacy is engaged in preparation of small volume parenteral solutions. The Skin Bank Fluid, a refrigerator and cooperation between the different departments—Surgery, Pharmacy and Bacteriology—are the main necessities to make

the program a success. The Skin Bank Fluid is prepared from a stock solution "Sterile Balanced Salt Solution 10x" containing phenol red as *p*H indicator. The method of preparation and suggestions about techniques and equipment to use to manufacture the several required solutions will be given next.

Methods of Preparation

General suggestions. (1) All chemicals used should be of analytical grade. (2) Throughout the preparation of all the solutions, strictest aseptic technique is required. Only steam-sterilized equipment is used, which is wrapped accordingly. To prevent contamination of beakers, graduates, etc. during the preparation, they should be covered whenever possible using the sterile material they were originally wrapped with. (3) All Water for Injection U.S.P. used for preparing the solutions or for rinsing the bacterial filtration assembly is previously adjusted to a *p*H of approximately 6.8. (4) The solutions are sterilized by filtration only, using as bacterial filter a sterile Selas porcelain candle (porosity 02, length of filter 8 inches, diameter 1 inch, without metallic attachment). Prior to use, the candle, connected by a one-hole rubber stopper with a glass mantle, and the receiving flask are rinsed 3 times with 200 ml. Water for Injection, using the suction line. (5) The first 20 ml. of any solution filtered through the water-rinsed Selas candle are to be discarded. (6) As containers, use clear, sterile Type I glass multiple dose vials (serum vials), close them with sterile diaphragm rubber stoppers and seal with aluminium caps. (7) Vials filled are inspected immediately for clarity. (8) Sterility tests are carried out according to the requirements of the *United States Pharmacopeia XV*. Samples are taken before, during and at the end of the filling operation, selecting vials from the lot chosen for filling. A part of the collected liquid may be taken for *p*H testing; the optimum *p*H of the preparation is between 6.8 and 6.9. (9) Fluid Thioglycollate U.S.P. XV serves as culture medium; the seeded medium is incubated for at least 7 days at 30°-32°C. (10) The finished containers are properly labeled and stored at refrigerator temperature of 4°C; they may be released for use after negative readings of the seeded culture medium are obtained. (11) Records of the finished preparation should include the following data:

1. amount of liquid prepared;
2. amount and size of containers filled;
3. date of manufacture and name of pharmacist making the preparation;
4. *p*H measurements;
5. date, number and results of bacteriological cultures;

and in addition for the Skin Bank Fluid:

6. when using "outdated whole blood" the donor's name, registration number and blood group; (or when using Normal Human Plasma, irradiated, the manufacturer's name and the lot number);
7. expiration date and lot number of the sterile neomycin sulfate powder;
8. expiration date of the Skin Bank Fluid—six months after the day of manufacturing but not exceeding the expiration date of the neomycin sulfate.

Phenol Red Solution 0.2%

Phenol Red	0.24 Gm.
N/20 Sodium Hydroxide Solution	13.0 ml.
Water for Injection, to make	120.0 ml.

Procedure. Mix the phenol red and N/20 sodium hydroxide solution in a sterile 125 ml. beaker, bring to total volume of 120 ml. with the Water for Injection and add sufficient N/20 sodium hydroxide to adjust to *p*H 6.8.

Balanced Salt Solution (BSS) 10x

Sterile Stock Solution

Calcium Chloride	1.4 Gm.
Dextrose, Anhydrous	9.1 Gm.
Sodium Chloride	80.0 Gm.
Potassium Chloride	4.0 Gm.
Magnesium Sulfate • 7 H_2O	2.0 Gm.
Potassium Phosphate, Monobasic	0.6 Gm.
Sodium Phosphate, Dibasic • 7 H_2O	0.9 Gm.
Phenol Red Solution 0.2%	100.0 ml.
Water for Injection, to make	1,000.0 ml.

Procedure. Dissolve the calcium chloride in 200 ml. of Water for Injection using a sterile 250 ml. graduated beaker. Place the other ingredients in a sterile, graduated 1000 ml. beaker containing 100 ml. of phenol red solution 0.2% and 600 ml. of Water for Injection, stirring with a sterile glass rod until dissolved.

Constantly stirring, add the calcium chloride solution slowly to the second solution and make up to volume of 1000 ml. with Water for Injection. Filter the solution through the rinsed Selas 02 candle using suction line for fast filtration. Fill approximately 85 ml. of the solution into 100 ml. sterile serum vials. Take samples for sterility and *p*H tests. Apply sterile stoppers immediately, inspect, seal and label properly.

Eighty ml. of the BSS 10x will be used in preparing each 1000 ml. of Skin Bank Fluid.

Skin Bank Fluid (SBF), Sterile

Balanced Salt Solution, 10x	80.0 ml.
Water for Injection	670.0 ml.
Plasma AB^+ (or A^+)	200.0 ml.
Neomycin Sulfate Powder, Sterile	0.5 Gm.
Water for Injection	50.0 ml.

Procedure. 500 ml. of outdated whole blood obtained from the Blood Bank, preferably AB^+ type, is centrifuged for 30 minutes. 200 ml. of the cell-free plasma are decanted into a sterile graduated beaker.

Add the BSS 10x to the 670 ml. of Water for Injection in a sterile, graduated 1000 ml. beaker, add

the plasma and filter through a sterile Selas 02 candle. Take samples for sterility and *p*H tests using some of the 50 ml. serum vials from the lot which is used later on. Then slowly inject the sterile neomycin sulfate solution through the rubber tubing, first cleaning site of injection with 70% ethyl alcohol. Mix contents in receiving flask by carefully shaking. Fill fluid into 50 ml. serum vials, apply sterile stoppers, inspect seal and label as:

Skin Bank Fluid
Use entire contents for each
jar of skin.
Keep in a cool place
Control..... Expir. Date.....

During the early storage of the SBF in the refrigerator the fibrinogen of the plasma is apt to cause turbidity which leads to the formation of a fibrin clot. This clot does not adversely affect the efficacy of the fluid. If desired, clotting can be avoided by keeping the decanted plasma at a temperature of -1°C. for five hours. Fibrin-like cakes form in the serum liquid. After separation, the serum so obtained has two advantages: (1) the filtration of the SBF is easier and faster and (2) only a slight precipitate, if any, will form in the stored fluid.

Variations of the Skin Bank Fluid

Instead of adding plasma or serum obtained from outdated whole blood, irradiated Normal Human Plasma may be used without changing the formula given above. During storage only a slight precipitation occurred.

Another possibility is the use of Human Serum Albumin; the formula may be changed to:

Balanced Salt Solution, 10x	80.0 ml.
Water for Injection	670.0 ml.
Human Serum Albumin	40.0 ml.
Dextrose 5% for Injection, USP	160.0 ml.
Neomycin Sulfate Powder, Sterile	0.5 Gm.
Water for Injection	50.0 ml.

The variations do not affect the desired *p*H of 6.8 to 6.9. No visible changes are observed during the storage period. However, at this time the report of the research institution engaged in testing the fluids for their qualifications has not yet been received.

Summary

The history of free skin transplantations is briefly discussed. The different types of cutaneous transplants, classified according to the donor, are mentioned. The need and usefulness of autografts and homografts are illustrated. Some methods of skin banking are listed. The establishment of a skin autograft and a skin homograft bank is mentioned, underlining the present limitations for storage, particularly in view of clinically conserving the cell viability of the preserved material, and the part which a hospital pharmacist can take in this matter.

The formula of the Skin Bank Fluid which is prepared by the University of Michigan Hospital Pharmacy Laboratory and employed at the University of Michigan Hospital Skin Bank, the equipment used, the procedure and test methods in preparing the medium, and the storage form of the final product are listed. Some variations of the original fluid are quoted, although the final laboratory results regarding their usefulness and superiority compared to the original medium, are not yet available.

In comparison with various clinical banks so far developed, the skin bank seems to be the one where a hospital pharmacist can take an active part in its establishment, and where the hospital pharmacist can assist in research and further development of preparations needed for this purpose.

The hospital pharmacist, thanks to his educational background and the greater facilities available in a hospital pharmacy, has a wide opportunity to render a much needed service to the medical staff and patients.

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SOVIET VIEWS AND PLANS about establishing an efficient system of pharmaceutical information

From an article by P. V. Lopatin and G. V. Lopatin*
adapted by Hubert Zacek

► AT PRESENT THERE IS NO SYSTEM OF SCIENTIFICALLY organized pharmaceutical information. Papers dealing with new drugs, and pharmacological, analytical, and pharmacognostical items are abstracted by chemical, biological, and medical journals and by issues of *Express-informatsiya* in the series *Zdravookhranenyie i meditsina* (Protection of Health and Medicine). On the other hand, problems of the technology of pharmaceutical preparations and of dosage forms, papers dealing with the storage of pharmaceutical preparations, pharmaceutical economics and administration etc., are covered very insufficiently by abstracting journals. Information bulletins of Main Directions of Pharmacies, another source of pharmaceutical information, are to be criticized because of their considerable conciseness which many times makes their efficient utilization impossible. The only Soviet journal destined for pharmacists—*Aptechnoe Delo*—has proved not to be sufficiently broad in its scope.

In view of all the above mentioned facts it is necessary to launch a pharmaceutical abstracting journal in the U.S.S.R. on the lines of already regularly published "Referativnyi zhurnal"s of chemistry, biology, etc. As the initial difficulties in starting such a journal would be immense, it would be worth while to initiate in the meantime a column of abstracts in the periodical *Aptechnoe Delo*. Another solution of the problem could be the insertion of the column titled "Pharmacy" into the "Referativnyi zhurnal" of medicine.

However, after forming a pharmaceutical abstracting journal there remain other tasks in order to provide a good pharmaceutical information service. In spite of all good properties of the above mentioned abstracting journal, there are some shortcomings *e.g.* insufficient coverage in the publication of abstracts, especially of those dealing with foreign papers and, furthermore, the fact that the scope of abstracts is limited. It thus seems necessary to publish a periodical containing information about new achievements of pharmaceutical science in a form that allows immediate use of ideas in practical work without the need of reading the original sources. The already mentioned *Express-informatsiya* could serve as an example of such a periodical. Of course, a particular column dealing with pharmacy should be established within the scope of this periodical.

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*Aptechnoe Delo 8, 3 : 48 (May-June) (1959): original title of the article "It is necessary to organize a system of scientific information."

With the formation of the two above mentioned organs there are connected such propositions as the establishment of efficient systems of classification of ideas of pharmaceutical interest, *i.e.* subject, formula, and author indexes. Naturally, still other devices making it as easy as possible to locate pharmaceutical information are necessary.

A third type of publication providing interested persons with information about innovations in pharmacy should be the publications of commercial institutions and also the periodicals edited by pharmaceutical faculties and research institutions.

There are some particular fields in pharmacy which should especially be given more attention by the services of pharmaceutical information. These fields follow from the planned development of national economy in the years 1959-1965:

1. Production of highly efficient medicinal substances (designed syntheses, promotion of rational compositions of medicinal preparations, phytopreparations, biogenic stimulators);

2. Improving the technology of dosage forms and galenic preparations (new ways of isolation of therapeutically effective substances from plants, utilization of atomic energy *e.g.* for sterilization, new dosage forms, pharmaceutical machines, etc.);

3. Studies on the storage of medicinal substances and dosage forms (influence of humidity, temperature, light, microorganisms, etc., packaging materials and machines, etc.);

4. Pharmaceutical analysis (new methods, organization of analytical work, new tools for analysis, etc.);

5. Commercial problems of pharmaceutical preparations (new ways of distribution of pharmaceutical preparations, organization of the network of pharmacies, information about new pharmaceutical preparations being available, etc.);

6. Organizational and economic problems of the pharmaceutical industry and pharmacies (need of pharmaceutical preparations, development of industry and pharmacies, work of pharmacists, etc.);

The information given about the above mentioned fields should possess the following attributes: (a) it should describe the achievements of pharmaceutical science and organization fully and objectively, (b) the information should be readily accessible to readers, (c) it should be up-to-date.

All the named facts suggest the necessity of forming a committee composed of representatives of pharmaceutical scientific institutes, industry, pharmacies, Ministry of Health of the U.S.S.R., and others whose proposition should be the realization of the above mentioned plans.

ABSTRACTS OF PAPERS

presented at the 19th International Congress of Pharmaceutical Sciences of the International Pharmaceutical Federation Zurich, Switzerland, September, 1959

ETHYLENE OXIDE STERILIZATION

Some Observations on the Sterilizing Effect of Ethylene Oxide, by N. Diding (Apotekens Kontrollaboratorium, Stockholm, Sweden.)

The author will describe a laboratory-scale sterilization procedure using a mixture of ethylene oxide and nitrogen as sterilizing agent. The technique has been used in studying the conditions for sterilization of contaminated plastic and glass bottles and medicines. All experiments are accomplished at 20° C and atmospheric pressure. The concentration of ethylene oxide was 1000 mg./L. The bactericidal activity was studied against various microorganisms, among other spores of *B. subtilis*.

From the experiments the following conclusions were drawn:

1. Bottles of plastic and glass bottles closed with a plastic lid were sterile within 12 hours exposure.
2. Sodium chloride tablets enclosed in plastic envelopes and 0.9% solution of sodium chloride, 1 cm. deep layer and contaminated with spores of *B. subtilis*, were sterile within 12 hours exposure.
3. A penicillin solution, 1 cm. deep layer, and contaminated with *E. coli* was sterile after 5 hours exposure without any notable decomposition of the penicillin.

The influence on some drugs in dry form, which were exposed to ethylene oxide, was also studied and will be discussed.

STABILITY STUDIES

The Correlation of Oven Testing with Field Storage, by G. R. Wilkinson (Allen & Hanbury Ltd., Ware, England.)

In order to set up laboratory methods for oven testing of products, concurrent tests have been made in ovens at various temperatures and also by sending the same products in similar packs to various places with various climates.

Samples returned at intervals have been compared with those stored in the ovens and comparisons have been made. Products where some active constituent could be assayed are given as illustration, as well as materials where only a subjective assessment could be made.

Conclusions have been drawn and suggestions made for further work.

STABILITY OF AMINOETHYL NITRATE

A Stability Study of Aminoethyl-Nitrate and Some Related Compounds with Special Reference to Pharmaceutical Preparations, by Birgitta Spross. (Pharmacia Ltd., Uppsala, Sweden.)

The following nitric acid esters of primary amino alcohols have been studied kinetically in dilute aqueous solutions: $O_2NO\text{-}(CH_2)_2\text{-}NH_2$ (I), $O_2NO\text{-}(CH_2)_3\text{-}NH_2$ (II), and $O_2NO\text{-}(CH_2)_4\text{-}NH_2$ (III), all as salts with p-toluenesulfonic acid.

The esters have been determined polarographically after removal of hydrolysis products and interfering anions by means of a strong anion exchanger. The assay is thus specific for the intact nitroxy group.

While the ratios between the found decomposition rates of (I) — (III) in 0.4 n HCl is 1:0.8:0.9, in 0.1 n NaOH they proved to be 1:0.08:13,000.

A more thorough study of (I) in various HCl, $HClO_4$, and HCl-NaCl media revealed that $O_2No\text{-}(CH_2)_2\text{-}NH_3^+$ in acid solution is subject to a hydrogen ion catalyzed hydrolysis. Because of the positive charge of the ester the primary salt effect is usually large.

The big difference between the rates of the different esters as determined in alkaline solution may be explained by a cyclic mechanism giving rise to 3-, 4-, and 5-membered imine rings in the first step of the hydrolysis of (I), (II), and (III), respectively. The rate constant is accordingly a true first order constant independent of the concentration of ester as well as of hydroxyl ion. A study of (I) in buffer solutions confirms the "imine mechanism," that dominates the hydrolysis down to pH values about 4.

The values of the Arrhenius' coefficients for the hydrolysis of the three esters have been determined in HCl as well as in NaOH. They confirm the postulated mechanisms.

Some applications on pharmaecutical dosage forms of (I), that is marketed by Pharmacia as a coronary vasodilator under the trade name of Nilatil, will be discussed. The results of sterilisation and storage tests on injections of (I) and the related diester $(O_2NO\text{-}CH_2CH_2)_2\text{-}NH$ (IV), and triester $(O_2NO\text{-}CH_2CH_2)_3\text{-}NH_2^+$ (V) are also briefly discussed.

RESERPINE STABILITY

On the Stability of Reserpine, by O. Weis-Fogh (Danmarks Apotekerforenings, Kontrollaboratorium, Copenhagen, Denmark.)

Under certain conditions reserpine is recognized as a very unstable substance. The purpose of the investigations was to study how reserpine is broken down under a variety of conditions in order to find out how to stabilize it in pharmaceutical preparations.

The investigations were mainly carried out on solution of reserpine and have shown that it can be stabilized in different ways. The breakdown products and the degree of destruction depend mainly on the solvent and on the storage conditions.

In one case it is shown that, under some conditions, a chemical may react as a stabilizer, under other conditions it accelerates the destruction.

MEASUREMENT OF ANTIOXIDANT ACTIVITY

The Determination of Diene Conjugation as an Evaluation of Antioxidants, by Tyo-taye Tukamato (Pharmaceutical School Nagoya City University, Nagoya, Japan.)

Various methods have hitherto been reported for measurement of antioxidant activity. These are all based on the measurement of peroxide or carbonyl value, or the amount of oxygen absorbed by the sample. A method of measuring diene conjugation is proposed as a more simple and accurate measure of the activity of antioxidants.

The proposed method is carried out as follows: A sample of linseed oil added with the antioxidant to be tested is heated on a water bath with passage of oxygen at a definite velocity. A definite aliquot of the oil is taken every hour and the conjugated diene formed is measured spectro-photometrically. The results so obtained agreed approximately with those of peroxide value and viscosity measurement.

ASSAY OF EPINEPHRINE

The Biological Assay of Adrenaline and Noradrenaline in Injections, by J. Morch (Royal Danish School of Pharmacy, Department of Pharmaceutical Biology and Department of Pharmacy, Copenhagen, Denmark.)

The blood pressure of the rat is proposed for the biological estimation of adrenaline and of noradrenaline in simple injections containing local anaesthetics. The rats are treated with a ganglion-blocking agent which obviates the need for spinalising, and the results compare favourably with those by other methods. The method is compared with a colorimetric and a fluorimetric method and it is shown to be the more specific. Injections of the following local anaesthetics are examined: procaine, tetracaine (amethocaine), lidocaine (lignocaine), cincaine (cinchocaine) and Carbocain.®

BLOOD pH

Clinical Significance of Blood pH-Determination, by M. J. Schulte (Stadtisches Krankenhaus, Arnhem, Holland.)

After a short explanation of the significance of the blood pH and the way in which it is determined at the clinical chemical laboratory, four examples are given of its clinical value. These are respectively: a case of respiratory acidosis, of metabolis acidosis, and of respiratory alkalosis, while finally the value of pH determination during heart operation under hibernation is explained.

EFFECT OF INSULIN ON HEART

Effect of Insulin on Heart in Situ of Cooled Homeotherm, by J. M. Radulović (Faculty of Agriculture, University, Belgrade, Yugoslavia.)

The subject of inquiry was the effect of insulin on various functional states of heart in situ of cooled rat (asphyxic hypothermia).

Should the heart, owing to the prolonged spontaneous work or owing to the repeated effects of single and frequency inductive electric currents, show the signs of overtiredness (weak systole, irregular rhythm of contraction and the phenomenon of summation of heart contractions), perfusion of insulin through vena cava or directly into the heart increases the force of heart contractions, accelerates and restores the regular rhythm of heart work.

Summated extrasystoles and complete tetanuses provoked by electric currents, as signs of tiredness and functional weakness of heart, disappear after the administration of insulin.

The insulin (just as proved in case of treatment with glucose and vitamin B_1), when applied to the damaged and tired myocardium, in addition to other beneficial effects, resulted in the increased excitability of myocardium, in the prolonged refractory period and in the shortened latent period. Insulin produces a positive tonotropic effect on myocardium.

NEW ANTIBIOTIC

A New Antibiotic Developed in Haifa, by Friederike F. Auslander (Hillel Remedy Factory Ltd., Haifa, Israel.)

A sporulating bacillus which proved to be antagonistic to gram-positive organisms in the cross streak test has been by chance isolated in 1955. The extract of its culture, while exhibiting the same antibacterial spectrum, killed also Paramaecia by lysis. Subsequent experiments showed that *Entamoeba histolytica* was considerably more sensitive to this lytic action than Paramaecia.

In the following the isolation of this organism a mutant could be selected which differed from the original strain morphologically by filamentous growth and scanty spore formation and by a considerably higher lytic activity with regard to protozoa, whilst the antagonistic effect against bacteria was hardly changed.

On account of empirical data, obtained with the extract from the mother strain, it had been supposed that the active principle of this bacillus exerts, besides its antibiotic effects, also an organotropic one, controlling intestinal hypermotility by interfering with the action of histamine and/or acetylcholine. The effect of both intestinal motor substances was inhibited by the administration of the active bacterial substance to the isolated gut. The inhibition was reversible.

It could be expected that the oral administration of this active principle to patients suffering from intestinal amebiasis might have the two-fold effect observed experimentally, namely, an antibiotic one against *Entamoeba histolytica* and an organotropic one against the intestinal dysfunction caused by the parasites. Therefore, trials were carried out to administer it in tablets, in the first place to cases of chronic amebic colitis of long duration, where all other treatments had only transient effect or none at all, later on also to acute cases of intestinal amebiasis. During 15 to 20 days no untoward side effects were observed except, in some *rare* cases, a transient nausea.

Altogether 441 chronic cases have been treated. Within less than a week after commencing the treatment the symptoms began to subside and after about two weeks they had completely disappeared. If there were in the stools, at the start treatment, only large trophozoites present, there was usually no change within the first days. After about one week the large amebae were replaced by the non invasive dwarf form, morphologically similar to *Entamoeba hartmanni*, as recently described by *Burrows*. They were found sometimes in greater numbers than the original large ones and it took about 20 days until they disappeared. If cysts only were present in the beginning, they were soon replaced by large trophozoites which, in turn, changed later into the dwarf form. One case was of particular interest, as the patient had developed a marked eosinophilis during his disease, obviously as a reaction to an amebic allergen.

In 5 cases it was possible to perform complement fixation tests before and after treatment. Whilst all patients gave a strongly positive reaction in the beginning, 4 were negative after 3 weeks and one was still weakly positive. After an additional treatment of 10 days he, too, became negative.

19 patients out of the 441 chronic cases relapsed within a follow up period of 10 months. They all responded very well to a repeated treatment.

In acute cases (179) the clearance of the bowels from the parasites was much faster and without the interpolation of the dwarf stage. Amongst them, there were 6 relapses. They, too, were easily controlled by the same treatment.

The described treatment, tried up to now in a total of many hundreds cases of intestinal amebiasis appear to be equal in its antiparasitic action to the amebicides currently in use, but superior as far as an early relief of symptoms and absence of serious side effects are concerned. It proved to be efficacious even in such cases of chronic intestinal amebiasis where all the other treatments were of no avail.

SOLUBILIZING AGENTS

Solubilisation by Surface Active Agents, by H. S. Bean (Chelsea School of Pharmacy, Chelsea College of Science and Technology, London, England.)

Dilute soap solutions behave like normal electrolytes, whereas stronger soap solutions possess quite different properties, one of the most important of which is their ability to "solubilise" water-insoluble materials. The concentration at which any soap solution becomes capable of solubilisation is characteristic of that particular soap and is known as the "critical concentration for micelle formation." A micelle is an organised structure in the soap solution, and consists of an aggregation of soap molecules. The interior of the micelle behaves as if it were a liquid hydrocarbon droplet and in it will dissolve oils or water-insoluble materials. Partially water-soluble materials will be orientated with their hydrophobic groups towards the centre of the micelle and their hydrophilic groups towards or projecting into the water.

The surface-active micelle-forming solubilising agents have extensive application in pharmacy. They are used in the formulation of Lysol® and other disinfectants containing halogenated phenols, in the preparation of concentrated aromatic waters and in water-miscible preparations of oil-soluble vitamins.

Concentrated disinfectant solutions containing halogenated phenols can be prepared with the aid of soaps but the inherent antibacterial activity of the phenol may be suppressed by the solubilising agent, especially if the latter is present in excess. The bactericidal activity of disinfectants containing solubilised halogenated phenols is determined by the concentration of phenol in the aqueous phase and is independent of the total concentration in the system as a whole.

Palatable preparations of solubilised oils can be prepared. They are much less liable to oxidation than emulsified preparations of the same oil. As an aqueous dispersion of an oxygen-labile liquid is converted, by the addition of a solubilising agent, through emulsion to solution, the oxidation rate progressively decreases.

U.S.P. ASSAY METHODS

Infrared and Ultraviolet Spectrophotometric Procedures in U.S.P. XVI, by A. Osol (Philadelphia College of Pharmacy and Science, Philadelphia, USA.)

The forthcoming revision of the United States Pharmacopeia (U.S.P. XVI) will provide infrared spectrophotometric identification tests for a considerable number of medicinals, both in bulk and in dosage forms; certain infrared assays may also be included. The several official methods for performing the tests, involving comparison with reference standards, will be described in detail.

U.S.P. XVI will retain most of the ultraviolet spectrophotometric procedures of U.S.P. XV, and add such tests for some of the new admissions. To eliminate the variables potentially existing in the U.S.P. XV methods, the new U.S.P. will require simultaneous comparison to be made with a reference standard grade of each medicinal agent thus tested. The detailed procedure will be reported.

VISCOTOXIN

Counter Current Distribution Studies on Viscotoxin, a Toxic Peptide from Viscum album L., by G. Samuelsson (Department of Pharmacognosy, Kungl. Farmaceutiska Institutet, Stockholm, Sweden.)

Viscotoxin from *Viscum album* has been investigated with the aid of ion exchangers and continuous paper electrophoresis. (*Samuelsson*, Svensk. farm. tidskr. 1959.) The substance is dialysable and electrophoretically homogeneous with an isoelectric point between pH 10.7 and 11.6. By paper chromatography the following amino acids were identified in hydrolysates of Viscotoxin: alanine, arginine, aspartic acid, cystine, glutamic acid, glycine, histidine, leucine and/or isoleucine, lysine, phenylalanine, proline, serine, threonine, tyrosine and valine.

Counter current distribution of Viscotoxin in the system 0.04 M *para*—toluene sulfonic acid/*sec*—butylalcohol showed the substance to be a mixture of several peptides. Because of the small differences in the partition coefficients the isolation of pure components was difficult. By repeated distribution experiments, some of which involved 2000 transfers, it was possible to purify the main component to such an extent that the experimentally found curve agreed fairly well with the theoretically calculated curve. Because of lack of material the other components could not be purified to that extent, but distribution ratios could be calculated for 3 other peptides, all of which were physiologically active as shown by their toxicity to mice. Some properties of the main component will be described.

PAPAVERINE-LIKE ACTION OF FLAVONOIDS

Studies on the Constituents of Pueraria-roots, a Chinese Drug Ko Ken and the Antispasmodic Action of Flavonoids and Anthraquinones, by Shoji Shibata, Takao Murakami, Masatoshi Harada, Yoshihiro Nishikawa, and Widagdo Budidarmo (Faculty of Pharmaceutical Sciences, University, Tokyo, and Faculty of Pharmacy, Chiba University, Japan.)

The *Pueraria*-roots are known in traditional Chinese medicine as a useful medicament whose especial principles, however, have not yet been reported.

The methanolic extracts of *Pueraria*-roots of Japanese and Chinese origin were fractionated by means of chromatography to obtain one non-fluorescent and nine violet-bluish fluorescent bands (*a* to *j* from bottom to top). The U.V.-spectra indicated that most of the components so far separated are isoflavone derivatives. The crystals separated from fractions *b* and *c* were proved to be daidzein (7,4'-dihydroxy-isoflavone) and its 7-glucoside, daidzin, respectively. The fraction *e* was a new isoflavone derivative having a polyalcoholic side chain and *f* was shown to be its xyloside. Daidzein showed an antagonistic action against acetylcholine by Magnus' method using mouse gut. This finding led us to investigate the papaverine-like action of other natural flavonoids and some related compounds. Of 37 flavonoids and 16 anthraquinones so far tested in comparison with papaverine hydrochloride (potency: 1.00), quercetin (2.62), kaempferol (2.46), fisetin (1.66), chrysosplenetin (0.76), daidzein (0.37), isoliquiritigenin (1.36), emodin (4.18), catenarin (2.03), norobtusin (0.84) and xanthopurpurin (0.85) showed remarkable activities.

ESTROGENIC ACTIVITY OF PENICILLIN

The Oestrogen Activity of Penicillium Mycelia, by Judith Kulcsár-Gergely (Pharmacological Department, Medical University, Debrecen, Hungary.)

We find data in the literature, that after administration of crystalline pencillin salt, short temporary cycle disregulation was to be observed. In animal experiments increased formation of epithelial pegs was found, but no oestrogen activity. Following the data on penicillin I made experiments with the mycelia of *Penicillium chrysogenium* examining their oestrogen and gonadotropic effects. The experiments were carried out on sexually mature, ovariectomized and on infantile rats. We used 5% and 10% watery extracts of mycelia, the extracts being obtained by extraction with light petroleum.

Watery extracts of mycelia shorten the sexual cycle of mature animals. This shortening is proportionally affecting every phase of the cycle. The extract causes oestrus on ovariectomized female rats. In the Allen-Doisy reaction the oestrus phase occurs suddenly without previous temporary phases. The presence of small amounts of gonadotropically active material was shown after preliminary treatment with small doses; a single large dosage caused oestrus in infantile rats.

After fractionation we found the dry residue of light petroleum-extract the most effective. It is soluble in 96% alcohol. This dry residue causes oestrus on ovariectomized rats. The effect of the aqueous mycelium extract is lasting. The extracts are toxic only in high concentrations and after evaporation over 50°.

ACTION OF HYDROGEN PEROXIDE

Effect of Hydrogen Peroxide on Hypertensive Rats, by M. J. Huston (Faculty of Pharmacy, University, Edmonton, Alberta, Canada.)

Rats were made hypertensive by subcutaneous implantation of desoxycorticosterone acetate pellets, removal of one kidney and administration of 1% sodium chloride as the drinking fluid. Hydrogen peroxide administered orally had the effect of reducing the hypertension and increasing the survival rate.

N.D.G.A.-ANTIOXIDANT

Determinations of N.D.G.A.-Antioxidant in Oily Vitamin Preparations, by A. Engelund (Danmarks Apotekerforenings Kontrollaboratorium, Copenhagen, Denmark.)

The chief purpose of the investigations carried out was to work out a simple method by which the contents of N.D.G.A. Antioxidant in oily vitamin preparations could be determined. The preparation examined was pills containing vitamin A and D in hydrogenated soy bean oil as vehicle and containing additionally 0.1% (i.e. 70 μg per pill) of N.D.G.A.

Both colorimetrical and chromatographic procedures were employed. Because of their lack of selectivity the former, however, were discarded and a chromatographic method was preferred. By means of the latter method the N.D.G.A. contents of pills can be detected with fairly close accuracy. It is rather selective, giving no or differing reactions with other antioxidants, and very sensitive giving a distinct reaction with about 1 μg of N.D.G.A. Further this method offers the advantage that it can be applied easily and without use of special apparatus.

ION EXCHANGE RESINS AND PYROGENS

The Action of Ion Exchange Resins on Pyrogens Part 2: The Effect of Deionising Plants on the Pyrogenicity of London Tap Water, by T. D. Whittet (Pharmaceutical Department, University College Hospital and Medical School, London, England.)

Experiments previously reported have shown that strongly basic anion exchange resins are capable of completely removing the pyrogenicity from London tap water and other pyrogenic solutions.

Since the commercially available deionising plants use these resins in that form, as part of the deionising process, it is possible that water from these plants might be apyrogenic. Before such deionised water could be considered for use in the preparation of injections it would be necessary to show that the plant always delivered pyrogen-free water when operated under the usual working conditions. A series of experiments has been carried out on variety of samples of deionised water from plants of various types.

The results show that, although deionising plants are capable of producing pyrogen-free water and usually do so, those at present available cannot be relied upon always to do so. Two-bed plants and mixed-bed column types generally give pyrogen-free water and would probably always do so if freshly regenerated each day. These plants also materially reduce the bacterial contamination of tap water. The cartridge-type mixed-bed plants, although giving water of very high chemical purity, were frequently found to give pyrogenic water.

The results obtained make it quite clear that specific conductivity or resistance, which have been claimed to give an indication of freedom from pyrogens, are completely useless for this purpose.

Samples of water with a very high specific resistance, or low specific conductivity obtained from cartridge-type mixed-bed plants, have often been found to be highly pyrogenic. These samples would have a greater chemical purity than freshly distilled water. On the other hand, samples from two-bed plants, which never have a specific resistance greater than one megohm and would therefore be unlikely to pass the chemical B.P. tests for purified water, are usually pyrogen-free.

The cautious attitude of the British and other pharmacopoeias in prohibiting the use of purified water for injection is justified, but it may eventually be possible to produce pyrogen-free purified water for injection by means of ion exchange resins. A plant is on the market in France which is claimed as giving pyrogen-free water suitable for the preparation of injections.

TO BE CONTINUED

A SERIOUS RESPONSIBILITY

guest editorial

by Robert P. Fischelis

► THE EXTENSIVE NEWSPAPER COVERAGE of the scandal growing out of the television quiz programs has some implications for pharmacy and the drug industry. Some units in the industry are of course involved directly, because they have been among the sponsors of the quiz programs now under fire. Such headlines as "Quiz Fake Aids Enemies of U.S."; "Anger, or Disgust, Seems to Rule Emotions in 'Quiz Whiz' Audience"; "Quiz Shows Double-Duped Public"; and others, reflect the general reaction of editors, columnists and writers.

The newspapers are having a field day at the expense of the television and radio industry. But one cannot help wondering to what extent most newspapers are really entitled to criticize the television industry, when one turns their pages and reads some of the advertising they carry. The same newspapers which are now preaching morality to their television competitors, who are implicated in what President Eisenhower has aptly described as "this whole mess," are guilty of carrying questionable advertising with extravagantly worded claims. To a certain extent, at least, it is the "pot calling the kettle black."

It is significant to note that it took some disgruntled loser to expose what was going on in these quiz programs. No regulatory agency or network took the initiative in exposing the deception. One can also speculate on the motivation of the Congressional investigation. Is it wholly in the interest of protecting the integrity of American institutions?

Now that it seems popular to go into the harrowing details of the hoax which has been perpetrated, the cry for action to clean up is voiced by a great anvil chorus, and the degree of punishment which should be meted out is being debated by all kinds of characters in all kinds of places.

What about the other public relations stunts, and the phony build-ups for people and institutions and products which have been going on all these years and have become worse as professional public relations experts have grown bolder and bolder. Top-flight executives, and people in high places who run industries, institutions and, yes, even churches, have been "sold" on the idea that one cannot do even an ordinary job any more without engaging "public relations counsel," whose business it has become to influence "opinion-moulders" on what to think and what is best for the future of these United States.

The integrity and honesty of producers and distributors of health products and acceptance of responsibility for their quality no longer seems to be sufficient for business or professional success. It appears that all of these qualifications must be buttressed by the "modern techniques" of advertising, publicity and public relations. This, we are told, is the way to assure acceptance of pharmacy's place in the sun by other members of the health team and by the public. There simply must be some ballyhoo.

There is much emphasis in high places on the observation that "honesty is the best *policy*," but very little on the fact that "honesty is best"—period.

This "whole mess" also raises the question of the extent to which government agencies can go in protecting the public against inaccurate claims in the marketing of food and drug products. A strict interpretation of the intent of the Federal Trade Commission Act and the Food, Drug and Cosmetic Act, as they relate to protection of the consumer against false claims, would hardly condone the advertising and distribution methods applied to some products which have been permitted to go directly to the public without medical advice or other protection. The fine print warnings on drug labels serve only as notices to the buyer to beware. The buyer, in most cases totally uneducated with respect to drugs, is expected to be the final judge as to whether the product will do him good or harm. The same righteous indignation manifested over the crooked TV shows could be helpfully applied to assist the consumer in counteracting the persuasiveness of the TV diagnosticians.

The "whole mess" goes much deeper than the quiz programs. Some of our more respected newspaper columnists have driven this point home rather strongly. One of these columnists says that "It has stirred the American people to look into themselves and into our national life." Another says "Haven't we, as a whole nation, gone very far toward the unstated creed that nothing is so important as winning, no matter how." Still another points out that "Foreign observers here are interpreting this as another proof of the confusion of intellectual and moral values of America."

The moral of all of this, as far as pharmacy and the drug industry are concerned, is that all of us owe a very great responsibility to the public. We must, indeed, be more than merchants with respect to the production and distribution of drugs, and we must remain, in every respect, above suspicion.

It is not in the public interest to apply high quality standards to the production of drugs while relaxing our ethics when it come to distribution techniques.

Unfortunately, every profession and vocation has its fringe operators. Members of our profession and industry who engage the service of public relations experts and utilize modern communication resources should bear in mind their ultimate responsibility for whatever may be produced in their behalf orally, visually or in print.

ROBERT P. FISCHELIS, formerly Secretary of the American Pharmaceutical Association is located in the Albee Building, 1426 G Street, N.W., Washington 5, D. C.

Therapeutic Trends

edited by WILLIAM JOHNSON

Imbretil—Muscle Relaxant

Imbretil, 1,6-hexamethylene-bis-carbaminoylcholine-bromide, is a long acting muscle relaxant synthesized in Austria. A clinical study in 573 anesthetized patients showed that the drug provides an excellent surgical field if muscular relaxation is required. Its greatest advantage is its ability to induce profound abdominal relaxation almost equivalent to that obtained with spinal anesthesia. Repeated doses were approximately four times as effective as the initial dose according to R. Dripps *et al* in *Anesthesiology 20*:646 (Sept.-Oct.) 1959. Imbretil, however, caused apnea or hypopnea in 29 of the 573 patients in the immediate postoperative period. Various antagonists used in 25 of these patients showed inconsistent and inconclusive results. The action of Imbretil may be compared to other relaxants of the depolarizing group. Its action is obviously slower in onset and much more prolonged in duration than that of succinylcholine. It seems to be a more reliable drug than decamethonium, however, in that abdominal muscular relaxation is dependable, profound and prolonged. The tachyphylaxis attributed to decamethonium was not seen with Imbretil. Imbretil is therefore a muscle relaxant somewhat slow in onset of action, powerful in its effect and longer acting than any other depolarizing relaxants in common use. This study was supported by the Burroughs Wellcome and Company.

WILLIAM JOHNSON

SC 8246—A New Estrogen Analog

SC 8246 (16 alpha chlorestrone 3 methyl ether), a new synthetic estrogen, was administered to 20 male survivors of acute myocardial infarction for periods varying from 6-12 months. The alpha:beta lipoprotein ratio, as determined by paper electrophoresis, increased significantly in 9 of the 10 patients in whom it was initially less than 20 percent. However, the total serum cholesterol decreased significantly in only 6 of the 13 patients in whom it was initially greater than 250 mg. percent. These effects on lipoprotein can, with rare exceptions, be accomplished without important side effects, except for mild gynecomastia. This is in contrast to standard estrogen therapy, in which significant gynecomastia and reduced or absent libido always occur when the dose is adequate to produce and maintain lipid shifts. Arthur Rivin in *Metabolism 8*:704 (Sept.) 1959 therefore states that if estrogens are to be used in men, SC 8246 appears to have a real advantage in terms of minimizing important side effects. SC 8246 was supplied by G. D. Searle and Company.

SYLVIA SCHMIDT

A New Repository Penicillin Salt

Some pharmacological aspects of alpha, beta, bis-(paradimethylamido-sulfonobenzyl-amino)-ethane · di-penicillin 6 have been noted in *Antibiot. Chemother. 9*:557 (Sept.) 1959, by S. Benviguati and F. Avanzini. Values obtained gave evidence that the new repository penicillin salt possesses a far lower toxicity than the other repository penicillin salts known up to now. Results of blood level studies after a single dose by subcutaneous administration in rabbits show that this compound is a repository salt and detectable levels are demonstrable for 72 to 96 hours. In comparison, procaine penicillin, because of its greater solubility, gave initially higher serum levels but was eliminated after 18 hours. Irritation tests showed this penicillin salt to have excellent local and general tolerance.

KENNETH W. HUCKENDUBLER

Antiseptic Activity of Beta-Amylose Triiodide

Studies were undertaken to indicate the germicidal activity of beta-amylose triiodide *in vivo* as relatively dilute solutions of this compound have been shown to have excellent germicidal ability *in vitro*. Unlike most germicides, blood serum or proteinaceous matter did not diminish the antibacterial activity of this compound. Very low toxicity and irritancy to the tissues resulted when germicidal concentrations were attained against all types of bacteria tested within the peritoneal cavity of mice. This study was done by Wallace L. Minto and Bernard Newman and reported in *Antibiot. and Chemother. 9*:530 (Sept.) 1959.

KENNETH W. HUCKENDUBLER

Dihydrostreptomycin Deafness

Thirty-two cases of permanent hearing loss after the use of dihydrostreptomycin were observed by Shambaugh *et al.* and reported in *J. Am. Med. Assoc. 170*:1657 (Aug.) 1959. Cases of irreversible hearing loss attributable to dihydrostreptomycin are continuing to occur, usually without the knowledge of the prescribing physician, because of the latent period of from several weeks to as long as six months between administration of the drug and onset of hearing loss. There is no known effective treatment for this type of nerve deafness. It was concluded by these workers that in view of the unique latent period before the onset of deafness, this antibiotic should be omitted from commercial combinations of antibiotics, or, if included, its presence should be clearly indicated in the name.

WILLIAM E. JOHNSON

Andro-Stanazole—New Anabolic Steroid

Andro-stanazole, (17 β-hydroxy 17a-methylandrostano (3,2c) pyrazole), has been evaluated for its nitrogen retaining and androgenic activities in castrated male rats. Orally it appears to be thirty times more anabolic and one-fourth as androgenic as methyltestosterone. Parenterally it appears to be one-twentieth as anabolic and one-fortieth as androgenic as testosterone propionate state Aaron Arnold *et al.* in the *Proc. Soc. Exptl. Biol. Med. 102*:184 (Oct.) 1959. Andro-stanazole is clearly an agent which merits further investigation for oral administration to patients under conditions where maximum anabolic action with minimum androgenic side effects is desired. The drug was supplied by Sterling-Winthrop Research Institute, Renssalear, N. Y.

SYLVIA SCHMIDT

Amphotericin B—For Prophylaxis Of Antibiotic-Induced Moniliasis

The importance of *Candida* as a significant pathogen has substantially increased with the advent of the antibiotic era. Although several possible explanations exist, it is generally conceded that a major factor in the development of any form of monilial infection following antibiotic therapy is the antibiotic-induced alteration of the patient's normal microbial flora. This alteration permits *Candida* to multiply rapidly, since they no longer need compete with the various bacteria comprising the normal flora. The greatest alterations in this normal flora are produced by the broad-spectrum antibiotics, and, since they are used orally, it is not surprising that their use enables *C. albicans* to flourish luxuriantly within the lower gastrointestinal tract. The results of a study by Stough *et al.* are reported in *Antibiot. Med. Clin. Therap. 7*:653 (Nov.) 1959 in which a group of more than 100 subjects were given a mixture of tetracycline five parts and amphotericin B one part. For each subject the total daily dose of tetracycline was 1.0 gram and that of amphotericin B was 200 mg. Amphotericin B is superior to nystatin in a pharmaceutical sense and it also has greater activity *in vitro* against various fungi. Considering the great potential for toxicity of intravenously administered amphotericin B, at least a partial explanation for the safety of this antibiotic, when administered orally, probably lies in its poor gastrointestinal absorption. Amphotericin B effectively checks and depresses any tetracycline-induced *C. albicans* overgrowth in the gastrointestinal tract; it does not interfere with tetracycline absorption from the gastrointestinal tract; and it is well tolerated and has not been observed to produce significant systemic toxicity.

WILLIAM E. JOHNSON

Thalidomide—New Hypnotic Drug

The hypnotic effects of thalidomide (Distaval), a nonbarbiturate sedative, have been compared to those of quinalbarbitone by a clinical trial in 24 patients suffering from acute psychiatric disorders with insomnia. Various checks suggest that the results are reliable. One hundred milligrams of thalidomide gave significantly longer sleep than 200 mg. of quinalbarbitone (secobarbital), but this dosage of quinalbarbitone gave longer sleep than 50 mg. of thalidomide. There was no significant difference between the drugs in the time required to fall asleep. No patient complained of hangover during the trial. C. E. Salter *et al.* in *J. of Clin. & Exper. Psychopathol. 20*:243 (July-Sept.) 1959 conclude that thalidomide is a potent and, within present experience, a satisfactory nonbarbiturate hypnotic, nontoxic to animals and free from narcotic or euphoric action. Weight for weight, it appears to have about three times the hypnotic potency of quinalbarbitone.

SYLVIA SCHMIDT

Relaxin—In Ulceration And Gangrene

Relaxin was used to treat two cases of severe Raynaud's phenomenon with associated trophic ulceration and gangrene. In the first case where the condition was caused by scleroderma-dermatomyositis, the lesions healed and moderate movement of the fingers returned with marked relief of pain. In the second case the condition was due to scleroderma and it was treated similarly with similar results. This study by Reynolds and Livingood appears in *A. M. A. Arch. Dermatol. 80*:407 (Oct.) 1959. While relaxin would not be the initial drug of choice, it would appear to be a useful adjunctive measure, and perhaps may offer something to patients who fail to respond to other forms of therapy. The relaxin for this study was supplied as Releasin by Warner-Chilcott Laboratories.

DALE R. HYDER

Timely Drugs

Alpha Chymar

GENERIC NAME: Alpha chymotrypsin.
INDICATIONS: Exerts a selective lytic action on zonule fibers of the lens; eliminates hazards of needling operation in intracapsular lens extraction.
DOSAGE: Detailed instructions for use in package brochure. Neither powder nor reconstituted solution should be autoclaved; solution should not be used if cloudy or contains a precipitate.
PREPARATIONS: Vials containing 1 mg. alpha chymotrypsin.
PACKAGING: Package containing 5 ml. vial of lyophilized alpha chymotrypsin with a 10 ml. vial of diluent; cartons of 5 packages.
SUPPLIER: Armour Pharmaceutical Co.

Cytoxan

GENERIC NAME: Cyclophosphamide; N,N-bis(*b*-chloro-ethyl)-N^1, O-propylenephosphoric acid ester diamide monohydrate.
INDICATIONS: Palliative agent in malignant neoplasms, particularly those arising from the reticuloendothelial and hematopoietic systems, and certain "solid tumors."
SIDE EFFECTS AND CONTRAINDICATIONS: Nausea and vomiting, alopecia (though not permanent), and dizziness.
DOSAGE: Orally, intravenously, intramuscularly, intraperitoneally, intrapleurally or directly into the tumor. Dosage must be individualized.
PREPARATIONS: Injection containing either 100 mg. cyclophosphamide with 45 mg. sodium chloride, or 200 mg. cyclophosphamide with 90 mg. sodium chloride; tablets of 50 mg.
PACKAGING: Injection, cartons of 12 vials; tablets, bottles of 100.
SUPPLIER: Mead Johnson.

Eskatrol

COMPOSITION: Dextro amphetamine (Dexedrine) sulfate and prochlorperazine (Compazine) dimaleate.
INDICATIONS: In overweight patients; controls appetite and causes relief from emotional stress associated with overeating and dieting.
SIDE EFFECTS AND CONTRAINDICATIONS: Chiefly, nervousness and insomnia; should be used with caution in presence of severe hypertension, advanced cardiovascular disease, or extreme excitability.
DOSAGE: One sustained action capsule (Spansule) daily, taken in the morning.
PREPARATIONS: Sustained release capsule (Spansule) containing 15 mg. dextro amphetamine sulfate and 7.5 mg. prochlorperazine dimaleate.
PACKAGING: Bottles of 30 and 250 capsules.
SUPPLIER: Smith, Kline & French Laboratories.

Griseofulvin Ayerst

CHEMICAL NAME: 7-Chloro-4:6-dimethoxycoumaran-3-one-2-spiro-1'-(2'-methoxy-6'-methylcyclohex-2'-en-4'one).
INDICATIONS: Treatment of mycotic infections of the skin, hair, and nails.
SIDE EFFECTS AND CONTRAINDICATIONS: Occasionally, gastrointestinal symptoms such as nausea, etc., headache, fatigue, lethary, mouth dryness or thirst.
DOSAGE: Adults, 0.25 Gm. four times daily or 0.5 Gm. twice daily; children, 0.25 to 1.0 Gm. daily depending on age and weight.
PREPARATIONS: Tablets containing 0.25 Gm. griseofulvin.
PACKAGING: Bottles of 30 and 100 tablets.
SUPPLIER: Ayerst Laboratories.

Levanil

GENERIC AND CHEMICAL NAMES: Ectylurea; 2-ethyl-cis-crotonylurea.
INDICATIONS: Mild, nonhabit-forming tranquilizing agent of low toxicity for relief of apprehension, tension and anxiety.
DOSAGE: Adults, 150 to 300 mg. three or four times daily, with 300 to 600 mg. at bedtime; children, 150 mg. three or four times daily.
PREPARATIONS: Tablets containing 300 mg. ectylurea.
PACKAGING: Bottles of 50 tablets.
SUPPLIER: Upjohn Co.

Resprogen

COMPOSITION: Adenovirus virus vaccine and influenza virus vaccine, aluminum phosphate adsorbed.
INDICATIONS: For protection against two classes of pathogenic respiratory agents with a single course of inoculations.
SIDE EFFECTS: Mild, local, and systemic reactions may occur.
DOSAGE: Adults, two intramuscular injections of 1 ml. each, at least two weeks apart.
PREPARATIONS: Each ml. contains 500 CCA units influenza virus, types A, A prime and B prime, together with types 3, 4 and 8 of adenoviruses in approximately equal parts.
PACKAGING: Vials containing 5 ml.
SUPPLIER: Parke, Davis & Co.

Terramycin Intramuscular Solution

COMPOSITION: Oxytetracycline (Terramycin) and lidocaine (Xylocaine).
INDICATIONS: In the treatment of diseases caused by susceptible organisms; contains a local anesthetic.
SIDE EFFECTS AND CONTRAINDICATIONS: Overgrowth of nonsusceptible organisms, particularly staphylococci.
DOSAGE: Single daily dose of 250 mg. or a dose of 100 mg. every 8 to 12 hours.
PREPARATIONS: Injection containing either 100 mg. oxytetracycline per 2 ml. or 250 mg. per 2 ml., with 2% lidocaine.
PACKAGING: Packages of 5 and 100 ampuls.
SUPPLIER: Pfizer Laboratories.

Consulting WITH BOWLES

GROVER C. BOWLES JR., *Baptist Memorial Hospital, Memphis, Tennessee*

► If narcotics are delivered to the nursing unit, must they be delivered by a pharmacist?

No. The delivery of narcotics may be entrusted to any reliable person. It is assumed that regardless of who delivers narcotics, sufficient control records are maintained so that any narcotics diverted between the pharmacy and the nursing stations would become known immediately.

► Do all hospitals charge for narcotics?

No. Charging for narcotics depends on individual hospital policy. Some hospitals include narcotics along with other stock drugs for which no specific charge is made to the patient. Other hospitals do not charge for routinely used narcotics but do make a charge for narcotics that must be obtained on special order. However, a great many hospitals do charge for all narcotic drugs administered.

► Could you suggest a method for sterilizing a solution containing morphine sulfate, ephedrine sulfate and scopolamine hydrobromide for intravenous use during eye surgery? What preservative do you suggest for this type of solution?

Solutions containing morphine sulfate, ephedrine sulfate and scopolamine hydrobromide may be sterilized by autoclaving or by bacterial filtration. If the solution is to be sterilized by autoclaving, certain precautions should be taken to avoid significant loss of potency. Overheating should be avoided. For solutions packaged in 20 ml. containers, 121° C. for ten minutes is sufficient to ensure sterility. The containers should be removed from the autoclave as soon as they can be safely handled. It is important that containers made of boro-silicate glass meeting the U. S. P. requirements for Type I glass be used. Soft glass containers may impart sufficient alkalinity to alter the *p*H of the solution and cause deterioration.

Chlorobutanol in a concentration of 0.5 percent is an effective preservative for this solution. The hydrolysis of chlorobutanol, which apparently takes place on heating, causes a lowering of the *p*H adding to the stability of the solution. It is generally felt that alkaloidal salts are most stable within a *p*H range of 3 to 4.8. Sodium chloride should be used to adjust the isotonicity of the solution and sodium bisulfite 0.1 percent may be added as an antitoxidant.

You will find the excellent article by John T. Murphy and Mitchell J. Stoklosa, "The Effect of Autoclaving on the Stability of Solutions of Certain Thermolabile Substances" published in *The Bulletin of the ASHP*, March-April, 1952, supplies much useful information about similar preparations.

► Can you supply us with any information about a new journal dealing with clinical pharmacology?

Clinical Pharmacology and Therapeutics, the official publication of the American Therapeutics Society, will be made available in January, 1960. It is supposed to be a comprehensive and authoritative journal devoted to pharmacology and therapeutics. It is to be published bimonthly by the C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. The annual subscription rate is $12.50.

► How are narcotic drugs for investigational use obtained and handled?

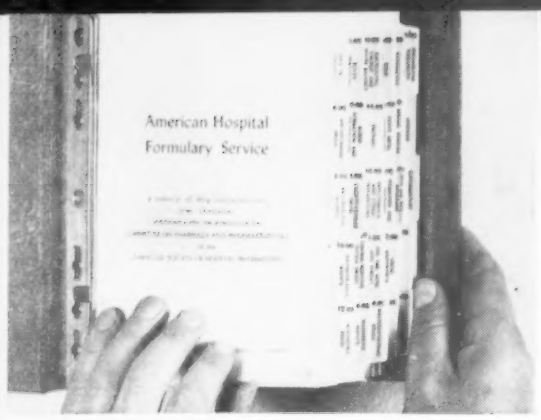
The same laws and regulations apply to the handling of narcotic drugs regardless of use. Thus narcotic drugs for investigational use must be obtained on the official narcotic order form (Treasury Department Form No. 2513), received, dispensed and accounted for in the same manner as for other narcotic drugs.

► What is a reasonable pharmacy inventory for a general hospital of 358 beds and 70 bassinets? Intravenous solutions are not included in the inventory.

Estimating what a specific pharmacy inventory should be, with any degree of accuracy, requires a thorough knowledge of the hospital, its location and the extent of pharmacy service provided. In the absence of this information, I should think that an inventory of approximately $25,000 would be entirely reasonable for the above hospital.

► Should a charge be made for handling and dispensing investigational drugs?

No. I think this is a professional service which hospital pharmacists should render to the investigator and the patient without charge. It is usually difficult to convince the investigator that investigational drugs should be dispensed by the pharmacy and one way to be sure that the pharmacy will be bypassed is to make a charge for this service. A possible exception might be when a special dosage form, such as a sterile solution, is prepared in the pharmacy.



AMERICAN HOSPITAL FORMULARY SERVICE

edited by WILLIAM HELLER, *Chairman ASHP Committee on Pharmacy and Pharmaceuticals*

Use Of A Drug List In Conjunction With Formulary Service

► IT IS DESIRABLE FOR EVERY PHYSICIAN ON A hospital staff to have a copy of the hospital's adaptation of the *American Hospital Formulary Service*. If this is not possible, an "abridged edition" or drug list can be a helpful supplement to the complete formulary. Those hospitals subscribing to the AHFS and which have previously had only a non-informational type formulary may find it advantageous to revise the list and continue using it as an "abridged edition" in conjunction with their AHFS adaptation.

The procedure as outlined above has proved successful at the University Hospital, University of Arkansas Medical Center. Until the time the AHFS became available, our hospital formulary consisted of a drug list. In adapting the AHFS to our needs, we decided that even though a copy of the complete formulary were placed on each nursing division, clinic station, and departmental office, it would still be desirable for each individual to have something immediately at hand when he simply wants to know what is available in the pharmacy.

The abridged edition of the UAMC Formulary is distributed to junior and senior medical students, to every physician on the faculty and staff, to pharmacy students taking a course in Prescription Practice, and even to non-clinical departments in the schools of medicine, pharmacy, and nursing. Copies are available on the hospital nursing units and in each clinic examining room. We made about 500 copies this year at a cost of 90 cents each in time and materials. This pocket-sized book is stenciled on 8½x14 paper so that the sheets may be cut in quarters to form the pages. They are then punched, collated, bound in heavy paper, and labeled as below:

UNIVERSITY OF ARKANSAS MEDICAL CENTER

HOSPITAL FORMULARY

ABRIDGED EDITION, 1959-60

For information on the physical and chemical properties, actions, uses, and dosage of these drugs, see the U.A.M.C. Hospital Formulary maintained on each nursing division and clinic station or call the Pharmacy Service, Ext. 413.

The abridged formulary is divided into three sections by using different colored paper. At the front, on yellow pages, is information for the physician and nurse; these pages have also been stenciled for insertion in the complete Formulary. They describe the membership, functions, and policies of the Pharmacy Committee of our hospital, discuss state and hospital regulations concerning prescription writing, and outline pharmacy policies affecting the physician and nurse. The Table of Contents concludes this section. In the second section, on green pages, are the nonproprietary names of drugs listed according to the pharmacologic-therapeutic index. Dosage forms are not included here. The white pages, which compose the third and major section, list alphabetically the drugs and preparations selected by our Pharmacy Committee. Drugs and dosage forms are listed under the nonproprietary name in the same style as under the section "Preparations" at the end of the AHFS monograph in the complete Formulary (except that preparations not underlined are not listed at all in the abridged book), e.g.:

SODIUM SALICYLATE

U.S.P.
Tablets, 300 mg.; enteric coated, 600 mg.

Synonyms and trade names are included in this alphabetical listing but the preparations are not listed thereunder. Instead, the reader is referred to the nonproprietary name via the same terminology as that used in the Index of the AHFS adaptation, e.g.:

Robaxin, brand of methocarbamol.

Every effort is made to be consistent with the AHFS in style and terminology.

While the pharmacy is responsible for keeping the AHFS adaptation on the floors and in the clinics up-to-date, this would be impossible with the abridged edition. Additions to and deletions from the formulary are published each month in the *Pharmacy Bulletin* in such a manner that they may be cut out and pasted on the back of the opposite page in the alphabetical section of the abridged edition. This is the responsibility

of the individual possessing the abridged formulary. A new abridged edition is prepared on the first of July of each year, when the house staff changes.

These two formularies supplement each other nicely. The abridged edition simply states which items are included in the formulary and the reader may look for them through the pharmacologic-therapeutic index or alphabetically by nonproprietary or trade name.

The hospital pharmacist of 1960, however, has not fulfilled his professional responsibility by merely telling the medical and nursing staffs which products he has available. As the all-around expert on drugs (comparatively speaking, since no one person can really be an all-around expert in this complex field), the pharmacist must provide information to the medical and nursing staffs to help them use these drugs most advantageously. This we do by use of the *American Hospital Formulary Service.*

One Binder Not Enough?

► SUBSCRIBERS who are using the *American Hospital Formulary Service in toto* as a complete drug reference have more material than can be contained in one binder. Even some hospital formularies may include more sheets than can easily be manipulated in the one binder.

The only answer to this is to use a larger binder or to divide the material into two volumes by using two binders. Extra copies of the binder are available from The Hamilton Press, Hamilton, Illinois, for $4.00 each. Although the binders now being supplied are slightly larger than those originally furnished, they too will soon be filled to capacity. Sooner or later you will need additional binders if you intend to keep all of the material in a reference book.

A special subcommittee of the Committee on Pharmacy and Pharmaceuticals has been investigating different binders for some time in the hope that we could find one which will hold even more material and/or be more easily manipulated. It appears that each type of binder has some advantages and disadvantages and we welcome our subscribers' suggestions concerning those characteristics which are most desirable and those on which they are more ready to compromise.

Supplements to AHFS

► THREE SUPPLEMENTS to the *American Hospital Formulary Service* were issued in 1959 and a fourth supplement will be mailed to all subscribers in February, 1960. Supplement pages can be identified by the copyright date which appears on each monograph. Also, a Supplementary Index appears with each mailing. The supplementary indexes are cumulative and earlier ones can be discarded with insertion of each new set. For identification, supplements carry the following dates:

Supplement 1: May 1959
Supplement 2: September 1959
Supplement 3: November 1959

Any subscriber who has not received these supplements should write directly to The Hamilton Press, Hamilton, Illinois, giving the name and address *as entered for the original* Formulary.

THE LAW of hospital pharmacy

edited by GEORGE F. ARCHAMBAULT

► *Because law is a complex specialty made so because of the existence of a set of Federal laws, 48 sets of state laws, and many county and municipal laws and regulations, the author of the column strongly recommends that when specific legal questions arise, one should always consult an attorney, competent in the local law.*

Qualifications of Users of Tax-Free Spirits

As a last word on the alcohol subject for now—are you and your administrator familiar with the March 18 and May 6, 1959 Industry Circulars of the Office of the Commissioner of Internal Revenue, Alcohol and Tobacco Tax Division? They involve your pharmacy and hospital if you use tax-free spirits (alcohol). For your information, we reproduce the circulars in full.

Industry Circular 59-12

QUALIFICATION OF USERS OF TAX-FREE SPIRITS CAUTION

Section 5271 I.R.C., as amended by Public Law 85-859, (72 Stat. 1370) provides that no person shall procure or use spirits free of tax on and after July 1, 1959, until he has filed an application to do so

Tax-free alcohol users and others concerned:

What applications should you file? In order to procure and use spirits free of tax (formerly called tax-free alcohol) on and after July, 1, 1959, you are required to make application on Form 2600, copies included, for an industrial use permit (formerly called a basic permit) to use spirits free of tax and an application on Form 1450 (Revised April 1959), copies included, for a permit to procure spirits free of tax.

What quantities should you show on your applications? Your application for an industrial use permit, Form 2600, requires that you state the quantity of tax-free spirits, including recovered tax-free spirits, that will be on hand, in transit, and unaccounted for at any one time. This quantity will determine the penal sum of your bond. It may be large enough to permit you to order containers of the size that you usually purchase and have the spirits in transit while you have a sufficient quantity on hand to care for your needs.

Your Form 1450 will require that you state the total quantity to be withdrawn during a calendar month and the quantity to be withdrawn during the term of the permit, considered to be one year. The proposed regulations state that the quantity to be withdrawn during any calendar month should not be more than one-twelfth of the annual requirements but provides that where you desire to withdraw more than one-twelfth of your annual quota during any month you should state your needs and furnish sufficient information for the assistant regional commissioner to determine whether such withdrawals should be authorized. If one-twelfth of your annual quota is less than a 55 gallon drum and you have sufficient reasons for desiring to purchase in a 55 gallon container, you should enter 55 gallons as the quantity to be withdrawn per calendar month and furnish sufficient information for the assistant regional commissioner to determine whether that portion of your application should be approved. The same procedure would hold true if you have a seasonal business that requires that you use tax-free spirits in only a few months during a year. You should determine your annual quota and the need for each of the few months that you expect to use the material and adequately explain your desires.

Period to be entered on Form 1450. Your entry for the beginning of the period should be July 1, 1959, but the ending date should be left blank at this time.

What should be done about your bond? You shall submit a new bond, Form 1448, or you may continue your current bond in effect by filing a consent of surety, Form 1533, copies attached, extending the terms of the bond to cover tax-free spirits on hand, in transit, and unaccounted for on and after July 1, 1959. If you have submitted a strengthening bond, such bond shall also be covered by a separate consent of surety. If you increase the quantity, you should submit a strengthening bond or a new bond.

Where and when qualifying documents should be filed. The above described applications and bond or consent of surety with the necessary supporting documents outlined in the accompanying excerpts from the proposed regulations shall be filed in duplicate with your assistant regional commissioner (alcohol and tobacco tax). They should be filed as soon as possible after you receive the forms in order to expedite handling in the office of your assistant regional commissioner.

Result if applications are not filed prior to July 1, 1959. If you do not file the two applications and bond or the consent of surety on your bond or bonds prior to July 1, 1959, you will not be entitled to use spirits free of tax on and after July 1, 1959, and the vendor named on your current withdrawal permit will be notified by the assistant regional commissioner that you many not continue to withdraw spirits free of tax.

Continuation of permits on and after July 1, 1959. The proposed regulations provide that if you hold a permit as a user, have a valid withdrawal permit on Form 1450 on June 30, 1959, and have filed the required applications, you may continue to use and withdraw specially denatured spirits on and after July 1, 1959, under such permits until final action is taken on your applications.

Inquiries. Inquiries in regard to this industry circular should refer to its number and be addressed to the office of your assistant regional commissioner (alcohol and tobacco tax).

DWIGHT E. AVIS
Director, Alcohol and Tobacco Tax Division

Industry Circular No. 59-12, Supp. No. 1

May 6, 1959

Purpose. The purpose of this supplement is to advise you of certain changes to be made in the instructions furnished you with Industry Circular No. 59-12.

Background. Reference was made in Industry Circular No. 59-12 to proposed regulations, and the instructions furnished contained excerpts from the proposed regulations. These proposed regulations were published in Part II of the Federal Register for April 21, 1959, as a notice of proposed rule making. During recent conferences with industry members and personnel from our regional offices suggestions were made for simplifying these proposed regulations. We believe that some of the suggestions are excellent, and we expect to propose their inclusion in the regulations. Accordingly, we have anticipated these changes and revised the earlier instructions. In filing your application you may follow the revised instructions. If, upon further review, additional information is found to be necessary, you will be so advised.

Information relative to changes in instructions and circular. (a) In listing your equipment, as required by paragraph 1 (f), it will be sufficient to list only the *principal* articles of equipment to be directly involved in the recovery and restoration of tax-free alochol.

(b) The information required in the first sentence of paragraph 1 (i) need not be submitted except on the specific request of the assistant regional commissioner.

(c) The second sentence of paragraph 1 (i) permits you to adopt, by reference, items of information on file in the office of the assistant regional commissioner and applies to all of the items of information required under paragraphs (d) through (h). This provision also applies to the documents listed under section 3, Organizational Documents.

(d) In lieu of the corporate documents listed in section 3 (a), only the following documents need be submitted.

(1) Certified true copy of the certificate of incorporation, or certified true copy of certificate authorizing the corporation to operate in the State where premises are located, if other than that in which incorporated.

(2) Certified list of the names and addresses of the officers and directors.

(3) Statement showing the number of shares of each class of stock or other evidence of ownership, authorized and outstanding, the par value thereof, and the voting rights of the respective owners or holders.

(e) You need not submit certified extracts or digests of minutes of meeting of boards of directors, authorizing certain individuals to sign for the corporation but your application must be accompanied by evidence which will establish the authority of the officer or other person who executes the application for permit to execute the same unless such authority is already on file in the office of the assistant regional commissioner.

(f) The names of the persons interested in a parent corporation, mentioned in the second sentence of paragraph 3 (c) (1), need be submitted only at the specific request of your assistant regional commissioner.

(g) In Industry Circular 59-12 in the paragraph entitled "Continuation of permits on and after July 1, 1959" the words "specially denatured" are incorrect and should be changed to "tax-free."

Modification of Form 2600. The use of a more specific term indicating the kind of spirits to be used is desired. Please modify Form 2600 by changing the word "spirits" to "alcohol" in the statement immediately above item 3.

Inquiries. If you have any questions regarding your qualification, they should be addressed to your assistant regional commissioner (alcohol and tobacco tax).

Important. If you have already filed your application in accordance with the first instructions furnished you, no further action is necessary.

DWIGHT E. AVIS
Director, Alcohol and Tobacco Tax Division

How To Use A Placebo

► THE QUESTION OF WHETHER A PLACEBO IS a physical or a psychologic form of treatment has caused much confusion. The answer seems to be that it is a psychologic form of treatment employing a physical substance. The moral problem of honesty that has clouded the issue and has often resulted in hedging and self-deception on the physician's part could be avoided if a psychologic frame of reference were explicitly acknowledged and used. This requires, however, that the physician be able to view psychotherapy as a legitimate and effective therapeutic measure. The selection of patients for treatment with a placebo should be based on the usual criteria for the selection of one or another psychologic technic. Since the placebo aims at the eradication of symptoms, it should not be employed when an etiologically-oriented therapeutic approach is feasible.

—**Marc H. Hollender, M.D. in *American Practitioner Digest of Treatment* (Feb.) 1958.**

News

NPC Annual Meeting

President Vernon O. Trygstad and Secretary Gloria Francke officially represented the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS at the Fifth Annual Luncheon meeting of the National Pharmaceutical Council held in New York City on December 10. Other hospital pharmacists attending included Don E. Francke, Editor of the AMERICAN JOURNAL OF HOSPITAL PHARMACY and Norman Baker, Apothecary-in-Chief at The New York Hospital. Dr. August H. Groeschel, Associate Director of The New York Hospital and Dr. John V. Connorton, Executive Director of the Greater New York Hospital Association, were also present.

Highlighting the program was announcement of new officers of the National Pharmaceutical Council and newly elected President Nelson M. Gampfer's Address in which he outlined plans for the coming year. Speaking of hospital pharmacy, he stated that inquiry and cooperation with pharmacy leaders will be continued in 1960 with the following further comment:

". . . We recognize the hospital pharmacist as an important member of the health team. We commend highly the progress made by the hospital pharmacists and the favorable recognition they have gained for our profession. We shall continue to promote good public relations in behalf of total pharmacy so that the people whom we serve may know us by our deeds. We shall continue to promote that which is best for the profession of pharmacy."

Hospital Pharmacy Represented at National Pharmaceutical Council's Fifth Annual Luncheon. Shown in photograph are (l. to r.) William E. Woods, NPC Assistant to the Executive Vice President as director of hospital relations; Don E. Francke, Editor of the American Journal of Hospital Pharmacy; Gloria N. Francke, Secretary of the ASHP; Vernon O. Trygstad, President of the ASHP; and Alfred C. Scott of the Upjohn Company, Chairman of the NPC Hospital Pharmacy Committee

In addition to naming Nelson M. Gampfer, Chairman of The Wm. S. Merrell Company, as President of the National Pharmaceutical Council, Newell Stewart was re-elected Executive Vice-President. Newly elected vice presidents include Foster B. Whitlock, President of Ortho Pharmaceutical Corporation, and John G. Bill, President of Merck Sharp and Dohme. Paul Gerden, Secretary and General Counsel of Abbott Laboratories, and Henry S. McNeil, President of McNeil Laboratories, Inc., were re-elected as vice presidents.

Also re-elected were Wilbur E. Powers, Secretary; L. J. Sichel, Vice President and Counsel of Ciba Pharmaceutical Products, Inc., Treasurer; and Franklin P. O'Brien, Vice President of G. D. Searle & Co., Executive Committee Chairman.

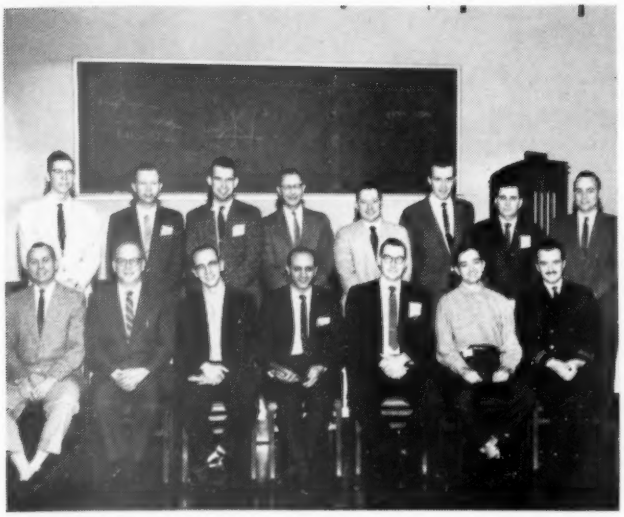
A.Ph.A. Officers-Elect Named

Ronald V. Robertson, practicing pharmacist from Spokane, Wash., has been elected President of the American Pharmaceutical Association for the 1960-1961 term. The First Vice-President-Elect is Robert J. Gillespie, practicing pharmacist of St. Joseph, Mich., and the Second Vice-President-Elect is John J. Dugan, practicing pharmacist of New Haven, Conn. Members-Elect of the A.Ph.A. Council for a term of three years are Roy A. Bowers, pharmaceutical educator of Newark, N. J., Louis J. Fischl, practicing pharmacist of Oakland, Calif., and Linwood F. Tice, pharmaceutical educator of Philadelphia, Pa.

The officers elected will be installed at the conclusion of the A.Ph.A. Annual Meeting in Washington, D. C., the week of August 14, 1960. The present officers of the A.Ph.A. who will continue to serve through the annual meeting next year are: Howard C. Newton of Boston, Mass., President; Leo F. Godley of Fort Worth, Texas, First Vice-President; and Paul W. Wilcox of West Point, Pa., Second Vice-President.

Officers of the American Pharmaceutical Association are elected in a mail ballot by all members in good standing, and the votes are counted by a Board of Canvassers appointed by the President. The Board of Canvassers, consisting of Chairman Noel E. Foss of Baltimore, Md., John E. Donaldson of Washington, D. C., and Ralph M. Ware of Richmond, Va., met at A.Ph.A. Headquarters on Monday, December 21, 1959, to tally the votes and certify the results of the election.

The Honorary President of the A.Ph.A. is elected by the House of Delegates annually, and the Secretary and Treasurer are elected triennially by the House of Delegates. Harry J. Loynd of Detroit, Mich., presently serves as Honorary President, while William S. Apple of Washington, D. C., was elected Secretary and Hugo H. Schaefer of Yonkers, N. Y., was elected Treasurer for a three-year term at the 1959 Annual Meeting.



U.S. Public Health Service Officers attending a course in Basic Radiological Health at the PHS Robert A. Taft Sanitary Engineering Center, in Cincinnati, December 7-18

PHS Pharmacists Participate in Radiological Course

Fourteen pharmacists from Public Health Service Hospitals from throughout the Nation participated in a Radiological Health Course presented December 7 to 18 at the PHS Robert A. Taft Sanitary Engineering Center, in Cincinnati. The Course was held under the auspices of the SEC Training Program and Radiological Health Training Activities, Division of Radiological Health, PHS Bureau of State Services.

Among the enrollees for the course were Peter L. Bogarosh, Aberdeen, S. D.; Carl H. Brown, Washington, D. C.; George R. Hall, Fort Defiance, Ariz.; Joseph P. Crisalli, Norfolk, Va.; M. Thomas Wagner, Jr., Staten Island, N. Y.; Bernard Shleien, Perry Point, Md., and Mark Barnett, Cincinnati; Walter J. Ludwig, Bethesda, Md.; Boyd W. Stephenson, Washington, D. C.; Ray D. Crossley, II, Bethesda, Md.; Robert E. McKay, Shawnee, Okla.; James E. Bleadingheiser, Perry Point, Md.; Allen J. Addison, Boston, Mass.; Samuel Merrill, Bethesda, Md.; and Frank W. Hollister, New Orleans, La. Mr. Barnett, Pharmacist Administrator, PHS Outpatient Clinic, Cincinnati, was a visitor during the course.

Competition for Historical Writing Announced

The Committee on Historical Records has set April 1, 1960, as the date on which all entries will be due in the competition in historical writing for hospital pharmacists conducted by the Committee in collaboration with the American Institute of the History of Pharmacy. This will permit time for evaluation of material and preparation of the awards that are to be presented at the annual meeting of the SOCIETY in Washington, D. C. in August. Awards are presented to the two hospital pharmacists submitting the best papers.

Hospital pharmacists are reminded that two types of projects have been suggested as good material to use in the preparation of entries:

1. Manuscripts on historical topics, such as the history of a hospital, of a hospital pharmacy, of a chapter of the ASHP, or some other organized activity, also significant are biographies of outstanding hospital pharmacists, either local or national.

2. Collection, identification, and classification of printed and manuscript documents that may be of later use in historical writing concerning hospital pharmacy and which may be on deposit with some library or organization or, even in a private collection. If the material itself cannot be submitted, a detailed description of it with a statement concerning the place of deposit should be submitted.

Chapter secretaries and local Committees on History of ASHP Chapters are invited to submit histories of their chapters.

Hospital pharmacists working on a project may obtain a complimentary copy of "Some Bibliographic Aids for Historical Writers in Pharmacy," by Glenn Sonnedecker and Alex Berman, on request to the American Institute of the History of Pharmacy, 356 Chemistry Building, Madison 6, Wisconsin. This brochure includes a section on hospital pharmacy.

Papers submitted in the competition should be sent to Adela Schneider, Southern Pacific Hospital, Houston, Texas.

► TERRY B. NICHOLS, Chief of Pharmacy Services at the Georgia Baptist Hospital in Atlanta, has been appointed Instructor in Hospital Pharmacy at Mercer University's Southern College of Pharmacy in Atlanta. Announcement of the appointment was made by Dean Oliver M. Littlejohn.

Mr. Nichols is a graduate of Howard College School of Pharmacy in Birmingham, Ala. He has held positions in the Veterans Administration Hospitals in Birmingham and in Thomasville, Ga.; at the Obion County General Hospital in Union City, Tenn.; and with the Miners Memorial Hospital Association in Washington, D. C.

► ROBERT C. BOGASH, Director of the Pharmacy Department at Lenox Hill Hospital in New York City and a past president of the ASHP, participated in a Hospital Purchasing Institute held at New York University-Bellevue Medical Center on December 11. As a member of a panel on "Pharmacy Purchasing Problems," Mr. Bogash served as the Pharmacist along with Solomon Seigel, Purchasing Agent, Jewish Chronic Disease Hospital in New York, and William Bold, Medical Service Representative of E. R. Squibb, New York. The Institute was sponsored by the New York Chapter of the American Association of Hospital Purchasing Agents.

as the president sees it—

VERNON O. TRYGSTAD, *Veterans Administration, Washington, D. C.*

► RECENTLY I heard a discussion by a hospital administrator on the responsibilities and liabilities of pharmacists in hospitals—more specifically, the responsibilities and liabilities of hospitals in the safe handling of drugs. With increasing numbers of more potent drugs in use in hospitals, it is difficult to imagine any hospital management permitting drugs to be purchased, stored, or dispensed by anyone other than a fully qualified pharmacist. Yet nearly half of the nation's hospitals permit this dangerous and costly practice. True, many of these are smaller hospitals. But as I see it, the patient in the small hospital is entitled to the same degree of protection and professional proficiency as the patient in a larger hospital.

I heard another prominent hospital administrator discuss the economics of pharmacy administration in the hospital. Asked what his answer would be to the hospital administrator who said he could not afford a pharmacist, his answer was to the effect that he could not afford to be without one. Proficiency in selecting and buying drugs, in managing drug inventories, in sound prescription pricing, and good professional judgment in discussing drugs with medical staff members can contribute immensely to the economy of the hospital as well as to the health and economic well being of the patient.

Why is it, then, that some hospitals do not have the services of a pharmacist, either on a full-time or part-time basis? Most frequently one of two reasons is given—cost, or unavailability of pharmacists. But in many hospitals that do not have the services of a pharmacist, drug dispensing duties are assigned to a nurse. I have heard for some time now of the critical shortage of nurses in most areas, and I believe too, that the cost of a professional nurse's time very nearly approaches that of a pharmacist. So even if it were professionally acceptable to assign pharmacy duties to nurses, it just does not make administrative good sense to do so.

How, then, can professional pharmacy services be made available in every hospital—to every hospital patient?

Obviously, our administrator friend who said he could not afford to be without a pharmacist would have one or more, occupied full-time. Of course there are hospitals so small that a pharmacist's time probably could not be utilized completely in purely pharmaceutical duties. A pharmacist, generally, is a pretty versatile person. His education and training have given him basic knowledge and skills which he can adapt to other technical duties in the hospital such as laboratory and x-ray. His business training and background, and his familiarity with many health care needs, in addition to drugs, make him readily adaptable to responsibilities in purchasing, supply, and general administration. Evidence of these capacities can be found in a number of hospitals today.

For those very small hospitals where funds or pharmacy work load appear to not justify employment of a full-time pharmacist, even with collateral duties, there are other means of assuring the advantages of professional pharmacy services—of eliminating the dangerous and costly practice of drug dispensing by non-pharmacists.

Part-time, or steady "relief work" has become a way of life in many smaller retail pharmacies where the regular pharmacist gets his time off without the prohibitive expense of a full-time second pharmacist. In many hospital pharmacies where the hours require additional pharmacy coverage, or in the small hospital where adequate pharmacy services can be provided in less than a full work day, part-time pharmacists also can be utilized to the advantage of the institution and the patients.

Where pharmacist's services are provided on a regular basis but not full-time, hospitals might want to designate such a pharmacist as "visiting" or "attending" pharmacists. This, perhaps would be more descriptive of his position, and similar to designations in other professions.

This past summer I talked with a pharmacist who had taken over the management of a hospital pharmacy in his home town, and was acting as pharmacy consultant to another hospital then under construction. When the new hospital is completed, he will also manage this second hospital pharmacy on a part-time basis. He fully expects to bring to this new hospital, proportionately the same savings in drug costs as he has

in his "full-time" hospital pharmacy through efficient purchasing and inventory management.

An article in the October 1 issue of *Hospitals,* Journal of the American Hospital Association, describes a contract arrangement whereby the pharmacy of a large hospital furnishes pharmacy services to a smaller one. Dramatic improvements in the efficiency and economy of drug management in the smaller hospital are reported.

I talked recently with a successful retail pharmacist who, along with his registered pharmacist partner, provides pharmacy services on a part-time basis to their small community hospital. These two pharmacists, who are retained by the hospital on a part-time salary basis, do all of the drug buying and dispensing for the hospital, and all profits or savings accrue to the benefit of the hospital and its patients. The salary received by these pharmacists is nominal—a relatively unimportant part of their income, I am sure. But they consider their work a contribution to their community and, incidentally, it adds considerably to the professional prestige of the pharmacists for their vital part in helping to serve the health care needs of the community.

For any hospital or pharmacist considering an arrangement for part-time pharmacy services in the hospital, the *Suggested Principles of Relationship between Smaller Hospitals and Part-Time Pharmacists,* which has been approved by the American Hospital Association and the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS may serve as a valuable guide. It is available from the Division of Hospital Pharmacy of the American Pharmaceutical Association, Washington, D.C.

It should be the goal of all of organized pharmacy—national, state, and local—and of every pharmacist, to assure that the best and safest pharmacy services are available to all patients in all hospitals not just in the larger ones. This in no way is an effort to create employment for hospital pharmacists. We need more hospital pharmacists for the jobs now available, but this should not diminish our interest in proper pharmacy services for all. This again emphasizes, however, our need to interest young pharmacists in a career in hospital pharmacy, and to provide adequate hospital pharmacy education and training.

Many smaller hospitals may welcome the assistance of pharmacists in the community, but is it available? I would hope that wherever the need exists, pharmacists in both hospital and retail practice will recognize it as their professional responsibility to make their services available, when requested, with the objective of assuring safe, efficient pharmacy service for all patients.

Vernon Trygstad

News

ASHP Officers-Elect Named

Clifton J. Latiolais

Peter Solyom

Clifton J. Latiolais, Director of Hospital Pharmacy and Assistant Professor at the Ohio State University Health Center, Columbus, Ohio, has been elected President of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS for the 1960-1961 term. The Vice-President-Elect is Peter Solyom, Chief Pharmacist at the University of Chicago Clinics, Chicago. These newly elected officers will be installed during the Annual Meeting of the SOCIETY which will be held in Washington, D. C. in August, 1960. Both the Treasurer, Sister Mary Berenice, S.S.M., and the Secretary, Gloria Francke, are currently serving three year terms.

President-Elect Clifton Latiolais is well known to ASHP members having served continuously as a member of the Executive Committee for the past three terms. Also, during the 1958-1959 term, he served as Vice-President of the SOCIETY, and is currently Chairman of the SOCIETY's Committee on Program and Public Relations. Since 1953, he has been a member of the editorial staff of the AMERICAN JOURNAL OF HOSPITAL PHARMACY The Vice-President-Elect has served the national organization as a member of several committees and is currently active on the Committee on Radio-Pharmaceuticals. He has been active in assisting with the InIstitutes which are held at the University of Chicago and has participated in the local pharmacy organizations. He has served as Secretary-Treasurer of the Chicago Branch of the A.Ph.A. and is currently a member of the Executive Council of the Illinois Society of Hospital Pharmacists.

The ballots of the recent election were counted by a Board of Canvassers, consisting of four ASHP members appointed by President Vernon Trygstad. Included on the Board of Canvassers were R. David Anderson, King's Daughters' Hospital, Staunton, Va.; Kenneth E. Hanson, U. S. Public Health Service, Washington, D. C.; Robert E. Lawson, University Hospital, Baltimore, Md.; and Robert Simons Memorial Hospital, Wilmington, Del.

News

Joseph Crisalli (center, right) receives plaque from Frank Hollister, President of the Louisiana Society of Hospital Pharmacists

Joseph P. Crisalli Honored

Mr. Joseph P. Crisalli of the U. S. Public Health Service Hospital in Norfolk, Va., was recently awarded a plaque by the New Orleans Branch of the American Pharmaceutical Association and the Louisiana Society of Hospital Pharmacists. The award cited Mr. Crisalli's service to the two organizations during the period from 1955 until 1958 when he resided in New Orleans and served as president of both the A.Ph.A. Branch and the ASHP Chapter.

Presentation of the plaque was made by Frank W. Hollister, now Pharmacist at the Public Health Service Hospital in New Orleans and president of the Louisiana Society of Hospital Pharmacists. The ceremony took place during a Radiological Health Course held in Cincinnati in December, with PHS pharmacists from throughout the country participating.

Oregon Dean Honored

Dr. Charles O. Wilson, recently appointed Dean of the Oregon State College School of Pharmacy, met an enthusiastic audience when he was feted at a "Meet the Dean" dinner sponsored by pharmacists of his adopted state in November. Hosts for the affair which attracted 215 pharmacists and guests were the Oregon Branch, American Pharmaceutical Association, and the Oregon Society of Hospital Pharmacists. Many pharmacy organizations in the state were co-sponsors of the event.

Dean Wilson told the pharmacists that he welcomes the support of all segments of pharmacy in the state and that the school needs this support. While expressing confidence in his teaching staff, he said that the physical plant in Corvallis is inadequate and emphasized the fact that the people of Oregon need a pharmacy school which is geared to teaching in the mid-twentieth century. He advocates inauguration of a Pharmacy Foundation in Oregon to encourage contributions from individuals and organizations friendly to the School.

Mr. E. Byron Smith, Chief Pharmacist at Good Samaritan Hospital in Portland, and Executive Secretary of the Oregon Branch of the A.Ph.A., served as Toastmaster. Also participating in an official capacity were Layke Seaton, President of the Oregon State Pharmaceutical Association, and Dr. A. L. Strand, President of Oregon State College at Corvallis.

Among the hospital pharmacists participating in the affair were Russell Austin, President of the Oregon Society of Hospital Pharmacists, who officially represented the group, and Robert Resare, Assistant Chief Pharmacist at Good Samaritan Hospital in Portland, who provided piano music for the social hour which preceded the dinner.

► JUSTIN L. POWERS, Director of Revision of the *National Formulary* and Editor of the *Journal of the American Pharmaceutical Association, Scientific Edition,* received the 1959 Remington Honor Medal at a dinner in his honor in New York on December 9. The Award, considered one of Pharmacy's highest honors, is presented by the New York Branch of the American Pharmaceutical Association. President Vernon O. Trygstad attended the dinner as a representative of the ASHP.

► A NATIONAL ADVISORY COMMISSION on Careers in Pharmacy has been activated by the American Pharmaceutical Association to assist the centralized recruitment activity recently established at A.Ph.A. Headquarters in Washington, D. C. The AMERICAN SOCIETY OF HOSPITAL PHARMACISTS is one of a number of pharmaceutical organizations which have been invited to membership in the Commission.

► THE SECOND ANNUAL National Industrial Pharmaceutical Research Conference will be held at Land O'Lakes, Wis., June 12-15, 1960. The preliminary program for the Conference, which is restricted to representatives of pharmaceutical industry and schools of pharmacy, has been announced by Louis W. Busse, Associate Dean of the University of Wisconsin School of Pharmacy, and Secretary of the Conference.

SELECTED PHARMACEUTICAL ABSTRACTS

and summaries of other articles interesting to hospital pharmacists

. . . . . .

edited by CLIFTON J. LATIOLAIS, HENRY J. DEREWICZ *and* LEO F. GODLEY

pH IN EAR INFECTIONS

External and Middle Ear Infections, (Editorial), J. Am. Med. Assoc. 171:554 (Oct. 3) 1959. (pH Factor in the Treatment of Otitis Media, Fabricans, N. D., Am. Med. Assoc., Arch. Otolaryng. 65:11-12 (Jan.) 1957).

The pH of solutions applied to the external auditory canal is an important factor in therapy in which the difference of two similar agents may be related to the ability of the agents to produce or enhance the state of alkalinity or acidity. The pH of the skin of the external ear of men and women is mainly acid and ranges from 5.0 to 7.8. Alteration of the acid pH to the alkaline side, as well as a moist environment containing cellular detritus and cerumen, present the greatest opportunity to bacteria and fungi for growth. These conditions are enhanced by the use of solutions on the alkaline side. In otitis externa, the pH is measured to be from 7.1 to 7.8. These findings emphasize the need for converting abnormal alkaline state of the external auditory canal in otitis externa to the desirable, normal, physiologic acid state.

NORMAN HO

URINARY EXCRETION DATA TO EVALUATE DRUG ABSORPTION

Nelson, E. and Schaldeman, I.: Urinary Excretion Kinetics for Evaluation of Drug Absorption I. Solution Rate Limited and Nonsolution of Aspirin and Benzyl Penicillin; Absorption Rate of Sulfaethylthiadiazole, J. Am. Pharm. Assoc., Sci. Ed. 48:489 (Sept.) 1959. (School of Pharmacy, University of California, San Francisco 22).

The use of urinary excretion data to evaluate drug absorption was discussed from the theoretical viewpoint and results of studies conducted to determine absorption of aspirin, benzyl penicillin, and sulfaethylthiadiazole were interpreted according to these considerations. It was shown that the absorption of aspirin was apparently rate-limited by the time necessary for this drug to dissolve *in vivo* and that benzyl penicillin absorption appeared to be rate limited by the intrinsic solution rate properties of the salts used. The absorption rate of sulfaethylthiadiazole was calculated by means of excretion rate data and the results obtained shown to be in excellent agreement with calculation of the same quantity made from previously reported blood level data. The calculated absorption rate of this drug was about 1,200 mg./hr., fifteen to thirty minutes after the injection of 1-gm. doses.

(Author's Summary)

GRAVIMETRIC ESTIMATION OF VANILLIN

A Note On Gravimetric Estimation Of Vanillin Via Its Semicarbazone, Kaistha, K. K., Drug Standards 27:141 (Sept.- Oct.) 1959. (State Control Drug Laboratory, Ambala Cantt., Punjab, India.)

The author had previously devised a gravimetric method for the estimation of camphor in pharmaceutical preparations via its semicarbazone and the specific conditions required for quantitative yield were described in detail. The author has satisfactorily extended application of the method to vanillin which contains an aldeyhde group. Vanillin is an official pharmacopeial substance listed in B.P. 1953; however no method for its estimation has been prescribed. In Appendix 1, B.P. 1948, vanillin is estimated by titrating an alcoholic solution of the sample with alcoholic potassium hydroxide. The method has proven to be unsatisfactory due to the end point being not very sharp. Other authors have described a gravimetric method for the estimation of vanillin using dinitrophenylhydrazine, but the results obtained by these methods have been reported higher by L. K. Sharp who instead had described two procedures: (a) a modified gravimetric method using dinitrophenylhydrazine and (b) a new volumetric method involving quantitative oxidation of vanillin by hydrogen peroxide in alkaline solution. The gravimetric method described by the author using semicarbazide hydrochloride, compares well with that of the modified gravimetric method using dinitrophenylhydrazine.

A. GORDON MOORE

QUANTITATIVE DETERMINATION OF CYANOCOBALAMIN

The Quantitative Determination of Cyanocobalamin, Cords, H., Ratycz, O T., Drug Standards 27:132 (Sept.-Oct.) 1959. (Squibb Institute for Medical Research, New Brunswick, New Jersey.)

A method is described for the quantitative determination of cyanocobalamin in solid and liquid vitamin B_{12} preparations having a cobalamin purity of over 30 percent and containing over 70 percent of the total B_{12} content in the form of cyanocobalamin. The total B_{12} concentration is measured by the light adsorption at 550 mu of a cyanide treated sample, and the cyanocobalamin/total B_{12} ratio is determined by quantitative paper chromatography. The limitations of the present official methods for the quantitative determination of cyanocobalamin are discussed.

AUTHOR'S SUMMARY

POLYVINYL ALCOHOL-BORATE-IODINE COMPLEX

A Study Of The Polyvinyl Alcohol-Borate-Iodine Complex I., Polyvinyl Alcohol-Boric Acid As An Indicator For Iodometric-Iodimetric Titrations, Monte-Bovi, A.J., Sciarra, J.J., Drug Standards 27:136 (Sept.-Oct.) 1959. (College of Pharmacy, St. John's University, Jamaica, N.Y.)

Solutions of polyvinyl alcohol and boric acid will change color in the presence of iodine. This solution changes from colorless to reddish blue depending upon the concentration of each component. This reaction was investigated in order to determine its application as an indicator for iodometric-iodimetric titrations in place of the usual starch indicator. Several preparations, including iodine, sodium thiosulfate, arsenic trioxide, mercurous chloride, ferric chloride solution, and copper sulfate were assayed by the official method, first by using starch as the indicator, and then through the use of a polyvinyl alcohol-boric acid solution as the indicator. In all cases the polyvinyl alcohol-boric acid indicator gave a satisfactory end point which was comparable to the end point detected by starch. These results indicate the polyvinyl alcohol-boric acid indicator may be used as a replacement for starch in iodometric-iodimetric titrations.

AUTHOR'S SUMMARY

ADRENALIN DETERMINATION

Influence of Copper and EDTA on the Alkaline Oxidation of Adrenaline, Harthon, J. G., J. Pharm. & Pharmacol. 11:553 (Sept.) 1959.

Adrenaline can be determined quantitatively in the presence of sulfite by measuring the maximum fluorescence obtained by oxidation in alkaline solution. The purpose of the investigation was to determine how the presence of copper influenced the fluorescence obtained in the determination of adrenaline based on its oxidation in strongly alkaline solution and to what extent the simultaneous presence of EDTA changed the fluorescence-time reaction. The presence of copper in the solution quenches the fluorescence. The presence of EDTA in Copper-free solutions has no influence on the fluorescence intensity curve. When copper is present as an EDTA-complex, however, the oxidation is strongly catalyzed and maximum fluorescence occurs earlier with higher and higher concentrations of complex. The reactions do not seem to be photochemically influenced.

THOMAS E. ARKINSON

BENZOCAINE DEGRADATION IN AQUEOUS SOLUTION

The Influence of Various Complexing Agents on Benzocaine Degradation in Aqueous Solution, Lach, J. L. and Pauli, W. A., Drug Standards 27:104 (July-Aug.) 1959. (State University of Iowa, College of Pharmacy, Iowa City, Iowa.)

The article describes the effects noted on the equilibrium solubility between benzocaine and its hydrolysis product, *p*-aminobenzoic acid and also the effects noted on the stability of benzocaine in aqueous solution when various complexing agents were introduced. In previous experimentation, since caffeine was the only agent investigated along these lines, this study represents an extension of these investigations to include the interactions of both micro and macro molecular agents and to compare quantitatively the inhibition of these various agents on the hydrolytic rate of benzocaine. Inhibition of the hydrolytic rate of benzocaine by the compounds employed was found to be less than that which has been reported for caffeine.

THOMAS E. ARKINSON

SURFACE ACTIVITY

The Surface Activity of 1,16-Hexadecane Disodium Sulfate at the Air:Water Interface, Elworthy, P. H., J. Pharm. and Pharmacol. 11:624 (Oct.) 1959 (Department of Physical Chemistry, School of Pharmacy, University of London, 29-39, Brunswick Square, London, W.C. 1).

The surface tensions of 1,16-hexadecane disodium sulfate in 0.001, 0.2 and 1.0 M 1. sodium chloride solutions have been determined by the Wilbemly method. Considerable aging effects were noted. The minimum molecular areas calculated were 95, 88 and 86 sq. A° respectively in the three salt solutions. The lowering of the surface tension was not as great as that caused by sodium dodecyl sulfate, and the hydrocarbon chain linking the two head groups in 1, 16-hexadecane disodium sulfate appeared to prevent very close packing in the surface layer.

AUTHOR'S SUMMARY

FILLERS IN DRY EXTRACTS

Fillers for the Dilution of Dry Extracts, Novikov, F. I., and Prosorovsky, A. S., Trade of Chemists (Apothec) U.S.S.R. 8:58 (1959). (Indian J. Pharm. 9:279 (Sept.) (1959).

Being highly hygroscopic, extracts of Belladonna and Adonis vernalis require fillers capable of absorbing large volumes of moisture with their dry state undisturbed. Dextrine possesses such properties. Maize dextrine is the best filler for extracts of Belladonna and Adonis vernalis since under normal storage conditions it retains its dry state for a year. Maize dextrine is a much cheaper filler than milk sugar. The most hygroscopic of all dextrines analyzed is that of wheat prepared by dextrinization at 180°C. during five hours. Maize dextrines obtained by roasting starch at 180°C. during five hours are the quickest to dilute. Of the potato dextrines, the most readily soluble one is that obtained by roasting during six hours at 180°C., while among wheat dextrines it is one obtained by roasting during five hours at 180°C. Preparations from extracts diluted with dextrine must be stored in tightly closed cans.

HENRY J. DEREWICZ

ADRENOCHROME DETERMINATION

Determination of Adrenochrome Mono-semicarbazone, Patel, A. A., Patel, J. L., Indian J. Pharm. 21:267 (Sept.) 1959. (Alnish Department, Alembic Chemical Works Co. Ltd., Baroda 2, India.)

A method is proposed for the determination of adrenochrome mono-semicarbazone (AMS). The method is based on the dark cherry color produced when sodium carbonate is added to AMS solution containing hydrochloric acid and sodium nitrite. The color is stable for about thirty minutes. The colored solution shows an absorption maximum at 430 mu and obeys Beer's law over a concentration range of 10 to 40 ug. The solution obtained by adding hydrochloric acid and sodium nitrite to AMS is colorless and is used as a blank. A description of the procedure to be followed is presented in addition to an application to the injection form of AMS. The method gave an average recovery of 99.6% with a standard deviation of ± 0.52.

HENRY J. DEREWICZ

8-HYDROXYQUINOLINE DETERMINATION

Estimation of Halogen Derivatives of 8-Hydroxyquinoline, Anantonarayanan, K. G., Kudalhar, V. G., Madiwale, M. S., Desai, H. H., and Walawalhar, M. B., Indian J. Pharm. 21:263 (Sept.) 1959. (Department of Pharmacology, Haffkine Institute, Bombay, India.)

A gravimetric method based on chelate formation has been developed for the determination of 5-chloro-7-iodo-8-hydroxyquinoline and 5, 7-di-iodo-8-hydroxyquinoline in pharmaceutical products. The method fundamentally consists of dissolving the sample to be determined in acetone and adding a solution of cadmium iodide in a known concentration. This mixture is then treated with sodium acetate to cause precipitation. Precipitation is followed by filtration and drying procedures. Variations are also presented in order to make the method applicable to various pharmaceutical dosage forms. Recoveries by this method were found to be 99.4 to 102.4 percent while recoveries by the U.S.P. method ranged from 93.6 to 165.8 percent. Even for complex mixtures reproducibility of results by the proposed method was satisfactory. The results indicate that the method is sufficiently specific, accurate and precise. It may therefore be adopted for routine estimation of these drugs even in the presence of chloroquine, some sulfonamides, most of the members of the B-complex group of vitamins and normal excipients of tablets.

HENRY J. DEREWICZ

CURRENT LITERATURE

. . . also calling your attention to the following articles appearing in recent hospital and pharmaceutical journals

. . . . . .

ADMINISTRATION

—Storage

Lapniewska, Janina: Storage of Drugs, Solutions and Equipment, *Hosp. Management* 89:78 (Jan.) 1960.

—Records

Heard, Jack S.: The Paperwork Side of Hospital Pharmacy, *Hospitals, J.A.H.A.* 33:62 (Dec. 1) 1959.

DETAILMEN

Willig, Sidney H.: The Detailman and the Hospital Pharmacist, *Hosp. Topics* 12:65 (Dec.) 1959.

EDUCATION AND TRAINING

Plein, E. M.: Hospital Pharmacy Is Going to College, *Modern Hosp.* 93:108 (Nov.) 1959.

NARCOTICS

Trygstad, V. O.: Control of Drugs on Nursing Units, *Hospitals, J.A.H.A.* 33:73 (Nov. 1) 1959.

OUTPATIENT PRESCRIPTIONS

Vance, Joe: Out-Patient and Retail Prescription Services: Are They Insurable? *Southern Hosp.* 27:54 (Nov.) 1959.

PROFESSIONAL RELATIONS (ETHICS)

Sister Cecelia Marie Peterman: Defining Pharmacy's Professional Ethics, *Hosp. Progress* 25:790 (Nov.) 1959.

SMALL HOSPITALS

Anon (Small Hospital Questions): Pharmacy and Therapeutics Committee Role, *Modern Hosp.* 93:57 (Nov.) 1959.

Sperandio, G.: The Retail Pharmacist and the Small Hospital, *Tile and Till* 45:opp. 106 (Nov.-Dec.) 1959.

GENERAL

Tiemann, K. E. and Lofgren, F. W.: Part II—Pharmacedures in the Pharmacy of a Hospital School, *Hosp. Management* 88:84 (Dec.) 1959.

DRUG EVALUATIONS

by the Council on Drugs of the American Medical Association

► THE FOLLOWING MONOGRAPHS and supplemental statements on drugs have been authorized by the Council on Drugs of the American Medical Association for publication and inclusion in *New and Nonofficial Drugs*. They are based upon the evaluation of available scientific data and reports of investigations. In order to make the material even more valuable, dosage forms and preparations of individual drugs have been added to the monographs. These dosage forms and preparations were not taken from material published in the *Journal of the American Medical Association* by the Council on Drugs; rather, they were obtained from such manufacturers' brochures, news releases, etc., which were available to us at the time of publication. An attempt has been made to make the list of dosage forms as complete as possible. However, no guarantee can be made that the list of preparations is complete and it is suggested that hospital pharmacists consult manufacturers' releases for additional dosage forms and preparations.

The issues of the *Journal of the American Medical Association* from which each monograph has been taken is noted under each monograph. Monographs in this issue of the JOURNAL include some of those published in the *A.M.A. Journal* for September 26, October 3, 10 and 17.

Notice

New and Nonofficial Drugs 1959 is now available from your local bookstore and from the publishers, J. B. Lippincott Company, Philadelphia, Pa. This 1959 edition contains monographs of drugs evaluated by the Council on Drugs of the American Medical Association and published in the Journal of the A.M.A. to January 1, 1959. The indexes listed below contain those drugs evaluated and published between December 20, 1958 and October 17, 1959.

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TO DRUGS EVALUATED IN THIS ISSUE

Index

TO EVALUATED DRUGS AND ARTICLES IN THE FEBRUARY, MARCH, APRIL, MAY, JUNE, JULY, AUGUST, SEPTEMBER, OCTOBER, NOVEMBER AND DECEMBER 1959 ISSUES OF THE AMERICAN JOURNAL OF HOSPITAL PHARMACY.

NEW AND NONOFFICIAL DRUGS

The following descriptions of drugs are based upon available evidence and do not in any case imply endorsement by the Council.

H. D. Kautz, M.D., *Secretary*

Amphotericin B — Fungizone®

Amphotericin B (Fungizone) is an antibiotic substance derived from strains of Streptomyces nodosus. The commercial preparation represents an amphotericin B-sodium desoxycholate complex.

Actions and Uses

Amphotericin B is an antibiotic agent which is used for the treatment of deep-seated mycotic infections. Its spectrum of activity against the yeast-like fungi, both in vitro and in vivo, appears to be wider than that of any other antifungal agent now available. Thus, included among the fungi against which amphotericin B is active are Coccidioides immitis, Histoplasma capsulatum, Cryptococcus neoformans, Blastomyces dermatitidis, Blastomyces brasiliensis, and species of Candida. It has no demonstrable effect on viruses, protozoa, or bacteria. Against susceptible yeasts and fungi, the drug is fungistatic rather than fungicidal. Amphotericin B is relatively insoluble in water and is poorly absorbed from the gastrointestinal tract. Hence, it should be given parenterally, despite a few reported instances in which deep mycoses responded to orally administered amphotericin B. The drug is very slowly excreted by the kidneys; demonstrable blood levels persist for 18 hours or more after the intravenous injection of a single dose. To date, there is no clinical evidence of acquired resistance by previously susceptible micro-organisms to the antifungal action of amphotericin B. However, resistance of Coccidioides immitus and some species of Candida can be developed in vitro. In the case of the Candida organisms, this is sometimes associated with cross resistance to nystatin.

Amphotericin B is effective against some mycotic infections which have been notoriously refractory to all previous modes of therapy. The most gratifying results have been obtained in patients with disseminated North American blastomycosis. In many cases, arrests and apparent cures of serious and widespread infections have been reported. Since it is more effective than stilbamidine or hydroxystilbamidine, amphotericin B will, no doubt, supplant the diamidine bases as the drug of choice for the treatment of serious pulmonary and systemic North American blastomycosis. Limited clinical data suggest that it many be equally effective in the South American variety of the disease.

Excellent results have followed the use of amphotericin B in many, but not all, patients with severe, disseminated histoplasmosis. This is in contrast to the uniformly disappointing results with other agents previously tried for the chemotherapy of this disease. Although detailed and prolonged follow-up studies will be necessary to determine its exact therapeutic value, the many arrests and apparent cures already reported indicate that amphotericin B is the drug of choice in disseminated histoplasmosis. The drug has been observed to cause sputum conversion in patients with chronic cavitary pulmonary histoplasmosis and may also prove useful in the recently described entity of mediastinal histoplasmosis.

The results of therapy in meningeal cryptococcosis (torulosis) have been less favorable than in blastomycosis or histoplasmosis. There have undoubtedly been some complete therapeutic failures. Nevertheless, amphotericin B has been shown to have a definite chemotherapeutic effect in numerous patients with the disease. To date, the most encouraging results have been obtained in patients with subacute cryptococcosis. Despite the inability to consistently detect appreciable concentrations of amphotericin B in the spinal fluid, some patients with cryptococcic meningitis have experienced

remissions of clinical symptoms, with a reversal of positive spinal fluid cultures after intravenous administration of the drug. It is too early to determine whether these cases represent cures. The drug has also been used intrathecally, with favorable results in some patients who did not respond to intravenous therapy. Although therapy with amphotericin B is not always effective, cryptococcic meningitis has responded favorably more often with this drug than with any previous agent. Currently, it should be the drug of first choice for this disease. In disseminated cryptococcosis without meningeal involvement, results have been better than in the meningeal form of the disease and are about equivalent to those obtained in blastomycosis and histoplasmosis.

Amphotericin B appears to be of some usefulness in the treatment of disseminated coccidioidomycosis. However, results have been quite variable. Some patients show no response whatever to the drug. Others, including a few with coccidioidal osteomyelitis, have been markedly benefited, with apparent arrest of the disease. It is still too early to determine whether coccidioidomycosis has actually been cured by amphotericin B. In view of the poor prognosis of disseminated coccidioidomycosis and the inadequacy of all other forms of therapy, a therapeutic trial of amphotericin B is indicated. The drug does represent a definite advance in the management of this disease. There is evidenc that amphotericin B given intravenously along with intrathecal therapy sometimes produces a better therapeutic response in patients with coccidioidal meningitis.

There is some evidence that generalized systemic moniliasis (candidiasis) may be favorably influenced by the use of amphotericin B. At the present time, however, clinical experience has been too limited to permit conclusions as to the ultimate effectiveness of the drug. Likewise, its relative usefulness against one species of Candida versus another is uncertain. Despite these inadequacies, however, it already seems apparent that amphotericin B is far more useful in systemic moniliasis than is nystatin. Although there is still good reason to seek better drugs, amphotericin B appears to be the most promising agent currently available for the treatment of this condition.

Toxicity and Side-effects.—The full spectrum of toxic manifestations to intravenously administered amphotericin B may not yet be characterized. Clinical experience indicates, however, that unpleasant and sometimes potentially dangerous side-reactions are almost inevitable at therapeutic dosage levels. Hence, amphotericin B should be used only in hospitals in which close clinical supervision of the patient is possible.

Systemic reactions, consisting of anorexia, headache, chills, and fever, are frequently encountered during the first few days of amphotericin B therapy. These tend to subside with continued administration and may be minimized by the concomitant use of antipyretics and/or antihistaminics. If a severe reaction occurs during the course of an infusion, therapy should be interrupted for about 15 minutes and then reinstituted. If the reaction recurs, therapy should be resumed at a lower dosage the next day.

The majority of patients show a rising level of blood urea nitrogen after prolonged therapy with the higher doses of amphotericin B. This toxic effect, together with other chemical evidence of renal dysfunction, is the chief limiting factor in the dosages which may be employed. Fortunately, to date, renal function has regularly returned to pretreatment levels after discontinuance of amphotericin B therapy. It follows, therefore, that blood urea nitrogen and nonprotein nitrogen levels should be checked routinely during therapy with amphotericin B. If the blood urea nitrogen or nonprotein nitrogen levels exceed 20 mg. per 100 ml. and 40 mg. per 100 ml., respectively, administration of amphotericin B should, in most cases, be stopped until these levels return to normal limits (usually one to two weeks). In some cases in which the clinical condition of the patient has warranted it, these values have been far exceeded, with no apparent evidence of permanent renal impairment. Kidney function tests should be done at appropriate intervals during prolonged therapy.

Solutions of amphotericin B have an irritating effect on the venous endothelium. Thus, pain at the site of infusion and chemical thrombophlebitis may follow its use. Thrombophlebitis may be minimized by decreasing the concentration of the infusion solution below 0.1 mg. per cubic centimeter, reducing the rate of infusion, frequent shift in sites of venipuncture, and using a smaller gauge needle. Among the miscellaneous side-effects to the drug are occasional instances of anemia during prolonged therapy and gastrointestinal cramping and diarrhea; a few patients have also developed a maculopapular drug rash.

In view of its appreciable toxicity, amphotericin B should be given only to patients in whom a diagnosis of susceptible mycotic infection has been reasonably substantiated, preferably by positive culture. There is not adequate justification for its use in vague and undiagnosed conditions merely because a skin test for one of the fungi may be positive. Once therapy has been initiated, quick cures should not be expected; prolonged therapy for a number of weeks or months may be necessary. The tendency to increase the dosage to the highest level recommended, or even higher, in the hope of obtaining a more prompt remission or cure should be discouraged. It is preferable to adjust the dosage to obviate renal damage and to prolong the time of treatment rather than to use higher dosages which are inherently accompanied by greater toxicity. The dosage may be so adjusted either by keeping below the maximal recommended daily dosage or, preferably, by administering the maximal daily dosage every other day.

Dosage

Although amphotericin B has been tried on an experimental basis by the oral route, by topical application, and by various other parenteral routes (intra-articular, intrapleural, intralesional, intramuscular), the drug is presently considered suitable for use only by slow intravenous infusion and, in coccidioidal meningitis, by intrathecal injection. For intravenous infusion, unless venous irritation or thrombophlebitis necessitates using a more dilute solution, concentrations of 0.1 mg. per cubic centimeter are generally employed. Such solutions are prepared from the sterile lyophilized powder by appropriate dilution with 5% dextrose in water for injection. Saline solution should not be used since it will cause the amphotericin B to precipitate. The rate of administration should be adjusted so that the total dose is infused over a three-to-six-hour period. For intrathecal injection, the dosage should be gradually increased up to a maximum of 0.7 mg. The drug is diluted with sterile water for injection to a final concentration of 0.25 mg. per cubic centimeter and then admixed in the syringe with spinal fluid. Intrathecal injections should be repeated every 24 to 48 hours.

Since tolerance to amphotericin B varies among individuals, dosage must be adjusted according to the specific response of each patient. Therapy is initiated with a daily dose of approximately 0.25 mg. per kilogram of body weight. This dose is gradually increased until an optimum level is attained. Generally, total daily dosage may range up to 1.0 mg. per kilogram. Within this range, dosage should be maintained at the highest level not accompanied by toxic manifestations. In seriously ill patients, who do not respond to doses of 1.0 mg. per kilogram of body weight, this dose may be exceeded cautiously and gradually up to a maximum of 1.5 mg. per kilogram, provided no significant toxic effects are encountered. Since amphotericin B is excreted very slowly, if necessary, therapy may be given on alternate days to patients on the higher dosage schedule. Under no circumstances should the total daily dosage exceed 1.5 mg. per kilogram of body weight. Whenever medication is interrupted for a period longer than seven days, therapy is resumed by starting with the lowest dosage level, i. e., 0.25 mg. per kilogram, and increased gradually to an optimum level as outlined previously.

When substantial improvement is observed, daily administration of amphotericin B may be substituted for therapy on alternate days. Duration of therapy is variable. In clinical

experience to date, significant improvement has been observed in most instances within four to eight weeks of treatment at full therapeutic dosage. A shorter period of therapy appears to produce a less favorable response and may lead to relapse.

Amphotericin B is heat labile and light sensitive. Hence both the dry powder and solutions of the drug should be stored in the refrigerator and protected against exposure to light. Unused solutions should be discarded after 24 hours.

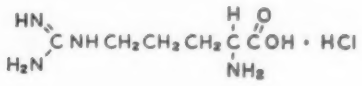
Preparations: powder (injection) 50 mg.
Year of introduction: 1958.
E. R. Squibb & Sons, Division of Olin Mathieson Chemical Corporation, cooperated by furnishing scientific data to aid in the evaluation of amphotericin B.
J. Am. Med. Assoc. 171:129/651 (Oct. 10) 1959.

Preparations

Injection Amphotericin B (Fungizone) 50 mg. vials.

Arginine Hydrochloride — Argivene® Hydrochloride

ARGININE HYDROCHLORIDE (Argivene) is L-arginine hydrochloride.—The structural formula of arginine hydrochloride may be represented as follows:



Actions and Uses

Arginine hydrochloride is an amino acid preparation with pharmacological actions and clinical uses similar to those of sodium glutamate. (See the monograph on sodium glutamate in New and Nonofficial Drugs.) Its intravenous administration causes a lowering of blood ammonia levels. This effect is of very limited usefulness for the symptomatic management of gravely ill patients with encephalopathies associated with ammoniacal azotemia, usually the result of severe liver dysfunction (so-called hepatic coma). Although the drug has no effect on the course of the liver disease itself, its ability to lower blood ammonia levels may bring about a reversion of the neurological status from stupor to consciousness. As in the case of sodium glutamate, symptomatic improvement with arginine hydrochloride seems to be most pronounced in those patients whose comatose condition has been precipitated by circulatory nitrogenous loads of exogenous origin. The proper management of hepatic encephalopathies with hyperammoniemia includes a low-protein intake, antibiotics given orally, evacuation of the gastrointestinal tract, and dextrose infusions. Hence, the intravenous use of arginine hydrochloride in such cases is considered an adjunct to other measures designed to lower blood ammonia levels.

Ammoniemia is sometimes observed in such other conditions as congestive heart failure, severe infections, anoxic states, shock, certain types of poisoning, metabolic acidosis (including diabetic coma) and erythroblastosis fetalis. It is doubtful, however, that these conditions are positive indications for arginine infusions.

Arginine hydrochloride is sodium-free and, hence, is better tolerated than equivalent amounts of sodium glutamate. The chief hazard to its use is associated with the presence of the chloride ion in the salt. Thus, the drug should be used with caution in patients with hyperchloremic acidosis, especially in the presence of renal disease or anuria.

Dosage

Arginine hydrochloride is administered intravenously. A solution containing 20 Gm. of the drug in 50 cc. of water is diluted with 500 to 1000 cc. of 5 to 10% dextrose in water for injection. This diluted solution is then infused by intravenous drip over a period of four hours.

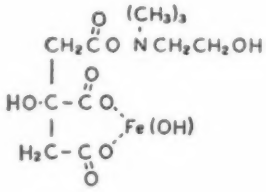
Preparations: solution (injection) 20 Gm. in 50 cc.
Year of introduction: 1957.
Gray Pharmaceutical Company, Inc., cooperated by furnishing scientific data to aid in the evaluation of arginine hydrochloride.
J. Am. Med. Assoc. 171:141/553 (Oct. 3) 1959.

Preparations

Injection Arginine (Argivene) Hydrochloride 0.4 Gm. per ml.; 50 ml. vials.

Ferrocholinate — Chel-Iron® Ferrolip®

FERROCHOLINATE (Chel-Iron, Ferrolip) is iron choline citrate chelate.—A chelate prepared by reacting equimolar quantities of freshly precipitated ferric hydroxide with choline dihydrogen citrate. The structural formula of ferrocholinate may be represented as follows:



Actions and Uses

Ferrocholinate is a hematinic agent which is used for the treatment of iron deficiency anemias. The iron of this preparation is present in a chelated form; i.e., the metallic ion is sequestered and firmly bound into a ring within the chelating molecule. This process apparently alters its toxic properties and the diffusion of the iron into the circulation. Thus, although ferrocholinate is much more soluble in water and digestive juices than either ferrous sulfate or ferrous gluconate, its acute toxicity is less. For example, doses of 200 to 250 mg. of elemental iron per kilogram of body weight, as the sulfate or gluconate, are fatal to rabbits and dogs, but the same dose of elemental iron as ferrocholinate is well tolerated in these animals. In addition to a lower acute toxicity, ferrocholinate also causes less gastrointestinal ulceration, vomiting, diarrhea, and weight loss in animals than does the same dose of iron as ferrous sulfate or ferrous gluconate.

Ferrocholinate is proposed for oral administration in the prevention and treatment of microcytic, hypochromic anemias due to iron deficiency. Such anemias may be the result of deficient iron intake, excessive loss of iron as in hemorrhage or heavy menstrual flow, or in infancy or pregnancy in which the demand for hemoglobin is increased. Clinical experience with ferrocholinate for any of these conditions has been very limited to date. Although preliminary studies would suggest that hematological responses are comparable to those previously attained from other iron preparations, more clinical experience is necessary to substantiate the ultimate usefulness of ferrocholinate as a hematinic agent.

The available clinical evidence, although meager, would appear to bear out the results of the laboratory toxicity experiments; that is, ferrocholinate seems to be better tolerated in the therapeutic dosage range than are ferrous sulfate and ferrous gluconate. In the small number of patients so far observed, complaints were limited to mild nausea, diarrhea, or constipation. These complaints tended to disappear on continuation of therapy, and in no case were they so severe as to require discontinuance of medication.

On the basis of these laboratory and clinical observations, ferrocholinate may have an advantage over other orally administered iron preparations from the standpoint of tolerance and danger of acute toxicity after overdosage. In terms of clinical efficacy, however, present evidence is inadequate to warrant such comparisons.

Dosage

Ferrocholinate is administered orally. For adults and children over six years of age, the proposed dose is 330 to 660 mg. three times daily. This amount supplies 120 to 240 mg. of elemental iron per day. For infants and children under six years of age, the proposed maintenance dose is 104 mg. (12.5 mg. of elemental iron) once a day; therapeutic dosage for such patients should be determined by the physician according to the severity of anemia present. Pending more clinical evidence to support the usefulness of ferrocholinate, the foregoing doses must be regarded as tentative.

Preparations: solution (oral) 208 mg. per cc.; syrup 33.2 mg. per cc.; tablets 330 mg.
Year of introduction: 1958.
Flint, Eaton & Company cooperated by furnishing scientific data to aid in the evaluation of ferrocholinate.
J. Am. Med. Assoc. **171:127/891 (Oct. 17) 1959.**

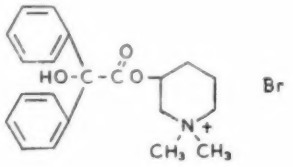
Preparations

Solution, Oral, Ferrocholinate (Chel-Iron; Ferrolip) 0.33 Gm. (iron choline citrate) per ml.; 30 ml. bottles.
Syrup Ferrocholinate (Ferrolip) 0.33 Gm. per 4 ml.
Tablets Ferrocholinate (Chel-Iron; Ferrolip) 0.33 Gm.

Mepenzolate Methylbromide

Cantil® Methylbromide

MEPENZOLATE METHYLBROMIDE (Cantil) is 1-methyl-3-piperidyl benzilate methylbromide.—The structural formula of mepenzolate methylbromide may be represented as follows:



Actions and Uses

Mepenzolate methylbromide is an anticholinergic compound that has been used chiefly for the relief of spasm and hypermotility associated with diseases of the lower gastrointestinal tract.

There is convincing evidence in experimental animals that mepenzolate methylbromide, in common with other atropine-like agents, is highly active and relatively specific in antagonizing the effects of acetylcholine. It inhibits both spontaneous and chemically induced intestinal contractions. Reports differ on its relative effects on various segments of the gastrointestinal tract, but there is some evidence that it has a more pronounced and prolonged spasmolytic effect on the colon than on the higher portions of the gastrointestinal tract. It causes relaxation of the sphincter of Oddi and suppresses pancreatic secretion. Its actions on other organ systems are also typical of cholinergic blocking agents.

In human subjects, mepenzolate methylbromide inhibits the motility of the small intestine and, to a lesser degree, that of the stomach. The evidence concerning its effect on the colon is conflicting, some reports indicating a more significant reduction of colon motility than of the small intestine. It is reported to produce a definite reduction in the free hydrochloric acid and total volume of gastric secretion.

Mepenzolate methylbromide has proved useful in relieving the abdominal pain, gaseous distention, and diarrhea associated with diseases of the colon. It is more effective in functional conditions, such as the irritable bowel syndrome or spastic colon, in which it has been reported to be as effective as atropine and to compare favorably with the more acceptable synthetic anticholinergic agents. It may also provide some symptomatic improvement when used as an adjunct in the management of ulcerative colitis, regional ileitis, infectious diarrheas, and other inflammatory diseases of the intestinal tract.

Side-effects that have been observed include dryness of the mouth, blurred vision, dizziness, headache, and constipation. These may frequently be satisfactorily controlled by reducing the dosage. Difficulty of urination and urinary retention in the presence of prostatic hypertrophy are claimed to occur less frequently with mepenzolate methylbromide than with other anticholinergic drugs; these complications have, nevertheless, been reported.

Mepenzolate methylbromide is contraindicated in the presence of glaucoma, pyloric obstruction, and cardiospasm. It should be used with great caution in the presence of prostatic hypertrophy.

Dosage

Mepenzolate methylbromide is administrated orally. The optimal dosage should be carefully determined for each individual patient. For initiating therapy, 25 mg. four times daily may be tried. If the response is unsatisfactory, the dosage may be gradually increased until the desired therapeutic effect is obtained or until untoward symptoms intervene.

Preparations: tablets 25 mg.
Year of introduction: 1956.
Lakeside Laboratories, Inc., cooperated by furnishing scientific data to aid in the evaluation of mepenzolate methylbromide.
J. Am. Med. Assoc. **171:127/891 (Oct. 17) 1959.**

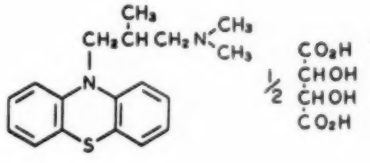
Preparations

Tablets Mepenzolate (Cantil) Methylbromide 25 mg.

Trimeprazine Tartrate

Temaril® Tartrate

TRIMEPRAZINE TARTRATE (Temaril) is 10-(3-dimethylamino-2-methylpropyl)phenothiazine tartrate.—The structural formula of trimeprazine tartrate may be represented as follows:



Actions and Uses

Trimeprazine tartrate is a phenothiazine compound which is structurally and pharmacologically related to promazine. It is identical in chemical structure to promazine except for the 2-methyl substituent in the propyl chain. As may be expected, trimeprazine exerts most of the actions of the phenothiazine derivatives, such as depression of the central and sympathetic nervous systems and counteraction of histamine. However, some of these actions, especially the antiemetic, hypotensive, and potentiating effects, are not as prominent as with other phenothiazine derivatives. On the other hand, the histamine-antagonizing action of trimeprazine is, depending upon the test and mode of administration, from one and one-half to five times as potent as that of promethazine, which is closely related chemically to trimeprazine.

Pharmacological studies in animals indicated possible areas of usefulness for trimeprazine in the treatment of allergic disorders and mental or emotional states. During early clinical testing, however, it became apparent that trimeprazine, in low dosage, exerted antipruritic action which was more pronounced than any of its other effects. Clinical evaluation demonstrated that trimeprazine was effective in relieving pruritus accompanying dermatoses of allergic, inflammatory, metabolic, hemovascular, and psychic origins. In addition, it was found useful in those dermatoses, such as dermatitis herpetiformis, whose etiology is not clearly understood. Although its mode of action is not known, trimeprazine appears to exert an antipruritic effect that is not directly related to its histamine antagonism or to its tranquilizing or sedative actions. Accordingly, trimeprazine has been recommended exclusively for the symptomatic treatment of mild and severe pruritus, whether acute or chronic. It often relieves itching which is not relieved by other therapies, and, in many cases, the administration of trimeprazine permits the reduction or elimination of concomitant topical and systemic medication. Presumably, this is made possible by interrupting the itch-scratch-itch cycle, which encourages healing of lesions.

In general, all of the precautions applicable to other phenothiazine compounds, such as promethazine and chlorpromazine, should be observed when using trimeprazine. Mild and transient drowsiness is the most frequently encountered side-effect; however, it disappears, in most cases, after several days of medication. The drug has not been shown to cause jaundice, but one case of agranulocytosis has been reported; no difficulty was encountered in reversing this disorder. Because such serious side-effects are seen with some phenothiazine derivatives, even though infrequently, patients receiving trimeprazine should be watched for their possible appearance. Since virtually all reported cases of agranulocytosis associated with administration of phenothiazine compounds have occurred between the fourth and tenth weeks of treatment (including the case just cited), patients on prolonged therapy should be observed particularly during that period.

Dosage

Trimeprazine tartrate is administered orally. Dosage should always be adjusted according to severity of the symptom and the response of the patient. The usual daily dosage for adults is 2.5 mg. four times daily or 5 mg. (as a sustained release capsule) every 12 hours. Resistant cases may require up to 30 or 40 mg. daily (nonambulatory patients with severe itching have received as much as 80 mg. in 24 hours with no ill-effects). The usual daily dosage for children up to the age of 2 years is 1.25 mg. at bedtime or, if needed, 1.25 mg. three times daily. Severe or refractory cases may require 1.25 mg. four times daily. The usual daily dosage for children 2 to 12 years of age is 2.5 mg. at bedtime or, if needed, 2.5 mg. three times daily. Severe or refractory cases may require 2.5 mg. four times daily. Total daily dosage should not exceed 5 mg. for children up to 2 years of age or 10 mg. for children 2 to 12 years of age. When itching is a nighttime problem, for adults or children, larger doses (5 or 10 mg.) should be administered at bedtime, with daytime dosage adjusted accordingly.

Preparations: capsules (sustained release) 5 mg.; syrup 0.5 mg. per cc.; tablets 2.5 mg.
Year introduction: 1958.
Smith Kline & French Laboratories cooperated by furnishing scientific data to aid in the evaluation of trimeprazine tartrate.
J. Am. Med. Assoc. 171:129/893 (Oct. 17) 1959.

Preparations

Capsules, Sustained Action, Trimeprazine (Temaril) Tartrate 5 mg. (Spansules).
Syrup Trimeprazine (Temaril) Tartrate 2.5 mg. per 5 ml.
Tablets Trimeprazine (Temaril) Tartrate 2.5 mg.

Methylphenidate Hydrochloride — Parenteral Use of

The Council has reviewed the available scientific evidence relating to the usefulness and safety of methylphenidate hydrochloride when administered by the subcutaneous, intramuscular, and intravenous routes. The oral use of this central nervous system stimulant has been described previously. (See the monograph on methylphenidate hydrochloride in New and Nonofficial Drugs.) Owing to a more rapid onset of action, the injectable form of the drug is better suited for use in emergency situations in which a prompt cortical stimulating effect is desired. Parenteral therapy is indicated also in patients who, for various reasons, may be unable to take oral medication and for uncooperative patients in whom it is important to assure that a full dose is received and retained. Presently available evidence indicates that parenterally administered methylphenidate (10 mg. one to three times daily or as a single dose of 20 to 30 mg.) is useful in overcoming the drowsinesss and lethargy sometimes produced by phenothiazine derivatives, rauwolfia alkaloids, barbiturates, anticonvulsants, and other sedative drugs. It may also be tried (30 to 50 mg. every 30 minutes as indicated), along with the usual supportive measures, for counteracting the signs and symptoms of acute overdosage of such agents. The drug has likewise been given parenterally (10 to 30 mg.) in the immediate postoperative period to hasten recovery from surgical and dental barbiturate anesthesia. As with the oral form of the drug, parenterally administered methylphenidate (10 to 20 mg.) can be used as a psychomotor stimulant in depressed, withdrawn, regressed individuals as a means of improving mood and behavior and for stimulating verbalization during psychiatric interviews. The dose for the latter purpose is 10 to 20 mg., given intramuscularly 10 to 15 minutes before the interview.

Whereas significant increases in blood pressure and pulse rate are rare when methylphenidate is administered orally, these occur not infrequently when the drug is given parenterally, especially by the intravenous route. Hence, parenteral therapy should be approached cautiously in patients with hypertension. In all patients, blood pressure should be checked before, and at frequent intervals after, each dose is injected. Other side-effects to the parenterally administered drug include occasional instances of nervousness, insomnia, anorexia, dizziness, palpitation, headache, nausea, and vomiting. Methylphenidate is contraindicated in patients with hyperexcitability and agitation and should be used cautiously in those with epilepsy.

Methylphenidate hydrochloride may be injected either subcutaneously, intramuscularly, or intravenously, the route chosen depending principally on the speed with which cortical stimulation is desired. Solutions for parenteral injection should be freshly prepared from the lyophilized powder, using the special solvent provided with each vial of the drug. Such solutions are pharmaceutically incompatible with a barbiturate or strongly alkaline solution and should not be injected through tubing or a syringe containing these agents.

The Council voted to amend New and Nonofficial Drugs to describe the parenteral use of methylphenidate hydrochloride.

Ciba Pharmaceutical Products, Inc., cooperated by furnishing scientific data to aid in the evaluation of the parenteral use of methylphenidate hydrochloride.

J. Am. Med. Assoc. 171:128/892 (Oct. 17) 1959.

REPORT TO THE COUNCIL

The Council has authorized publication of the following report. A review of the current status of knowledge of this important subject is offered as a guide to individualization rather than standardization in the application of specific immunological procedures to the management of tetanus-prone injuries.

H. D. KAUTZ, M.D., *Secretary*

SPECIFIC PROPHYLAXIS OF TETANUS

GEOFFREY EDSALL, M.D., Washington, D. C.

► ALTHOUGH THE INCIDENCE of tetanus in the United States has been decreasing during the past decade, several hundred cases still occur annually, in all walks of life and in all parts of the country.[1] The current situation has recently been well reviewed by Axnick and Alexander[1] who point out that, aside from the familiar hazard of tetanus after injuries and burns, there is still an unduly high incidence of the disease in relation to other circumstances, notably tetanus neonatorum.

Several publications on the management and prevention of tetanus have appeared within the past few years,[2] including an exhaustive review by Scheibel.[3] However, current literature and journal correspondence indicate that numerous areas of uncertainty persist regarding the prevention of tetanus. This status report attempts to assemble the existing basic knowledge on the subject, insofar as possible, and thereby to construct a rational set of procedures for the prophylaxis of tetanus. Necessarily, such a report on this complicated subject will be lengthy. For the convenience of the reader, the contents are summarized as follows.

Active and Passive Immunization

Prophylaxis against tetanus may be achieved by either active or passive immunization or, under certain specified circumstances, by a combination of both. The differences between these two ways of achieving protection deserve to be reemphasized. Passive immunization is ordinarily induced by the subcutaneous or intramuscular injection of purified antitoxic horse serum. The protection achieved is rapid but transient. Detectable antitoxin appears in the circulation usually within a matter of minutes, reaches a peak after 2 to 3 days, and generally disappears in 10 days or longer, depending on the dose administered and the rate of elimination or inactivation of the immune horse globulin, which is related to the reactivity of the patient to horse serum.

From the Division of Communicable Disease, Walter Reed Army Institute of Research.

Active immunization is a state achieved by injection of tetanus toxoid which acts as an antigen, stimulating the recipient to form his own antibodies. These, being autologous, are retained for a longer interval. Moreover, the production of new antibodies continues for a long period, and in addition such a process can be rapidly reactivated and greatly augmented by subsequent injections of toxoid. However, the initial development of significant antibody levels takes several weeks, so that immediate protection cannot be achieved by beginning active immunization.

Thus, passive immunization has the one advantage—sometimes a compelling one—of rapid effectiveness, but it has many disadvantages. The recipient of horse antitoxin not only makes no contribution to his own protection but actually reacts against it, by forming antibodies against the injected serum and thus accelerating its elimination. Severe anaphylactic reactions to the serum also occasionally occur. Moreover, an individual who has once been inoculated with horse serum (whether it was tetanus antitoxin or some other horse serum derivative) is likely to be sensitized against any horse serum preparation injected at a later date. This sensitization will generally lead to earlier and more marked serum sickness and will also lead to accelerated destruction of the antitoxin injected. In addition to these disadvantages, all of which limit the value of tetanus antitoxin, it is by no means entirely dependable as a prophylactic. Ever since World War I it has been well known that occasional cases of tetanus will occur in individuals given the standard prophylactic dose of tetanus antitoxin. Martini[4] cites two recent examples and summarizes many other similar reports. Still another important limitation to the usefulness of antitoxin is that it cannot protect against the considerable number of cases (reportedly as high as 50 to 60% of all cases of tetanus[5]) which occur in individuals whose injuries were so obscure or trivial that they were not treated by a physician. Finally, there is some evidence that the antibody resulting from active immunization is more effective, unit for unit, than that provided by passive immunization.[6]

Active immunization with tetanus toxoid, properly carried out, has essentially none of the disadvantage of passive prophylaxis. It is therefore the procedure of choice whenever it can be effectively employed, and it is widely practiced throughout the world.

Nevertheless, the prophylaxis of tetanus as currently practiced leads to a number of pertinent questions to which the practicing physician requires answers. The following questions are among those most commonly asked: 1. What is the actual degree of certainty that tetanus toxoid immunization, properly performed, will prevent tetanus? 2. How soon after completion of primary toxoid immunization (i.e., the first two or three injections, depending on the product and procedure employed) is a person immune to tetanus? 3. How long does this initial immunity last? 4. Should a reinforcing dose of toxoid be given and, if so, when? 5. How long does immunity last after basic immunization (i. e., primary immunization plus a reinforcing dose) is completed? 6. Are routine follow-up booster doses of toxoid indicated, and, if so, how often should they be given? 7. How long after a booster dose will a patient still be immune, and for how long will he remain capable of responding adequately and

promptly to an emergency booster dose of toxoid? 8. How rapid is this response? Is there a difference in the rate of response, depending upon whether fluid or precipitated toxoid is administered, or upon the interval since the last booster dose? 9. Are there circumstances in which an injured patient with a valid history of toxoid immunization should nevertheless be given antitoxin as well as toxoid? 10. In the unimmunized injured individual, when should prophylactic antitoxin be given, and what is the optimal dosage under the various conditions seen in practice? 11. In such a patient, is it practical to undertake simultaneous active immunization with tetanus toxoid?

For some of these questions, fairly direct answers are at hand. For most of them, however, there are no data from which an answer can be obtained directly. Decision must therefore be based, insofar as possible, on experimental observations, modified or interpreted in accordance with the physician's judgment as it applies to the particular case which confronts him.

Use and Effectiveness of Tetanus Toxoid in Routine Immunization

Reagents and Procedures.—Active immunization against tetanus may be carried out with fluid toxoid (FT) or precipitated toxoid (PT; this symbol will be used to refer without distinction to alum precipitated, aluminum hydroxide adsorbed [Alhydrox], and aluminum phosphate adsorbed preparations, since there appears to be little basis for making any significant immunological distinction between them). Active immunization may also be effected with pediatric preparations such as diphtheria and tetanus toxoids combined with pertussis vaccine (Dip-Pert-Tet, Triple Antigen) (DPT) or combined diphtheria and tetanus toxoids (DT); preparations primarily applicable to adolescents and adults, such as combined tetanus toxoid and typhoid-paratyphoid vaccine (TABT) used extensively by the Canadian, French, and Italian armed forces, and "tetanus-diphtheria toxoid, adult type" (Adult Dip-Tet) (TD),[7] now used by the American armed forces and coming into general use for adolescents and adult civilians in the United States whenever immunization against both tetanus and diphtheria is warranted.[8] A new preparation now recognized for pediatric use is one combining diphtheria, tetanus, pertussis, and poliomyelitis antigens[8a] (Quadrigen, Tetravax).

Indications for Active Immunization Against Tetanus.—The indications for active immunization against tetanus are manifold. The reason for its extensive use and the ways in which community-wide immunization can be approached have been superbly set forth in a special report by the London, Ontario, Academy of Medicine.[2g] Since the inoculation of tetanus toxoid is virtually free of side-effects, and since tetanus may occur in any human being, there is no actual contraindication to making tetanus immunization universal. However, since this ideal cannot readily be achieved in the immediate future, the physician can focus his efforts on those groups in whom tetanus immunization is especially indicated. Thus, Christensen[2e] recommends tetanus immunization for (1) all child health programs, industrial immunization programs, or other routine immunization programs reaching large groups; (2) allergic individuals and those who have had previous injections of antitoxin or any horse serum preparation; these persons are most likely to be sensitive to antitoxin and therefore may be unable to receive it when they need it most; (3) patients who have been previously treated for tetanus, and who may therefore get only very transient benefit from it because of their accelerated response against horse serum as a foreign protein (contrary to a widespread belief, such patients need active immunization against tetanus; since this disease does not immunize against itself, numerous cases of recurrent tetanus have been reported); (4) various groups subject to an apparently greater than average risk of tetanus-prone injuries, i. e., farmers, hunters, operators of heavy machinery, particularly in the open where injuries incurred may be contaminated with dirt; and (5) military personnel. Some would add to this list pregnant women, particularly those women living in areas where tetanus neonatorum is common. This proposal has been criticized on the ground that immunization of expectant mothers may make it more difficult to immunize the young infant against tetanus, due to the interfering effect of maternally transferred antitoxin.[9] However, this difficulty can be surmounted, as noted later.

Effectiveness of Tetanus Toxoid.—Experience gained primarily in World War II has provided overwhelming evidence that tetanus toxoid immunization, adequately carried out, is one of the most highly effective immunization procedures ever devised.[10] The tetanus rate in the U. S. Army, which in World War I was approximately 13 per 100,000 injuries and fell to the lower level of 2.4 per 100,000 during the period between World Wars I and II, was held to the incredibly low level of 0.44 per 100,000 injuries (12 cases in over 2,500,000 injuries) in World War II. Of these 12 cases, only 6 had had any toxoid injections, and only 4 of these had had basic immunization plus an emergency booster dose. Five deaths from tetanus occurred, of which two had received an emergency booster dose. This is truly a remarkable record, particularly when compared to the experience of the Japanese army, of German prisoners of war who, except for the Luftwaffe and paratroops, were not immunized, and of civilians in tetanus-prone areas where fighting was intense and civilian injuries were widespread. The tragic story of tetanus among Philippine civilians during the liberation of Manila[10c] provided a striking contrast to the absence of tetanus among the Americans who fought and suffered injuries under the same conditions.

Just how effective is tetanus toxoid? No active immunization procedure is wholly perfect, and even tetanus toxoid is no exception. Several apparently genuine failures to achieve protection with tetanus toxoid immunization have been reported (see table). Some are inadequately documented, some followed incomplete initial immunization, several occurred years after primary or basic immunization, and a few had received basic immunization plus a routine booster injection. However, there have been seven reported cases (all in military personnel) whose records indicated that they had received basis immunization, as well as an emergency booster at the time of injury. These reports show that tetanus can occur in an individual whose record indicates that he has been adequately immunized against tetanus. Nevertheless, the exceptional rarity of such cases, particularly in the American and Canadian armed forces, indicates that the hazard of tetanus in a properly immunized individual is far less significant than many other day-to-day risks arising in association with illness, injuries, and surgery.

Except for the aforementioned record of failures, all information regarding the effectiveness of tetanus toxoid—including studies on the efficacy of various injection schedules, on fluid versus precipitated toxoid, on the duration of immunity, and on the timing of booster doses—can be based only on antitoxin titrations of immunized subjects. What do these titrations actually mean? Numerous attempts have been made to correlate circulating antitoxin levels with the degree of protection obtained. Obviously, the question can be answered only by analogy from results in experimental animals. Most of the available and informative studies on the subject were summarized and discussed by Looney and others.[11] Many investigators have selected 0.1 unit of antitoxin per milliliter of serum as the "threshold of protection," usually by analogy with levels observed up to a week after injection of 1,500 units of antitoxin. However, it has been found experimentally that levels below 0.01 unit may be sufficient to protect animals from death, although symptoms have occasionally occurred at higher antitoxin levels. Indeed, the early observations of Ramon and Descombey in horses, over 30 years ago, suggested that antitoxin levels of about 0.001 unit will give protection, and a remarkable human experiment supports this concept. Wolters and Dehmel[12] injected themselves with a dose of tetanus toxin calculated

Tetanus in Immunized Persons

Author	Immunization Status	Cases, No.	Deaths, No.
Long[10a]	Primary only	2	0
	Routine booster 3 mo. previous	1	0
	Emergency booster	4	2
Hall[10b]	Uncertain	1	1
	Primary only	1	0
	Emergency booster	1	0
Moss[10d]	Primary and routine booster	2	1
	Emergency booster	1	0
Boyd[10e]	Primary* or incomplete	7	3
	Routine booster(s)	9	2
	Emergency booster	1	0
Stafford[10f]	Unconfirmed	2	0
Hedrick[10g]	Primary only	1	0
	Routine booster (date not given)	1	0
Boyer[10h]	Primary or incomplete	9	7
	1 booster, 3 yr. previous	1	1
Christensen[10i]	Primary, 10 yr. previous	1	0
	Unconfirmed	1	0

* Primary immunization in British army = 2 doses of fluid toxoid. Data based on British and Commonwealth troops only, as given in Boyd,[10e] table 4.

to be in the neighborhood of two to three human minimal lethal doses. At that time, each of them had a serum antitoxin level between 0.005 and 0.01 unit. Neither individual suffered significant symptoms after the inoculation, yet the amount of toxin given was sufficient to induce a booster response in each of them. Thus, despite the widespread acceptance of 0.1 unit as the "threshold of protection," there is very good reason to believe that a level of 0.01 unit or even lower is adequate.

Immunological Response to Tetanus Toxoid.—It is important to understand clearly the basic pattern of response which follows primary immunization and the subsequent administration of a reinforcing dose. The sequence of events has been vividly depicted by Evans,[13] whose findings may be summarized as follows. One month after the first injection the response was barely detectable, if at all. At this time a second dose was given. A fairly marked response occurred, the antitoxin level rising briefly to a peak titer averaging about 0.5 unit. However, at the end of about one year, the level had sunk to an average value somewhat below 0.1 unit. One-half of Evans' subjects were then given a third dose. Within 30 days their average antitoxin titer was close to 10 units. Most important, however, was the fact that one and one-half years later the subjects who had received a reinforcing dose still had levels averaging close to 0.4 unit, whereas those who had not received a reinforcing dose had fallen to an average of about 0.04 unit. Thus, the initial two doses, although they gave protection for upwards of a year, did not insure lasting protection. By contrast, the subjects who received a reinforcing dose at one year not only were well protected a year and a half later but possessed titers high enough to give a margin of protection for several years thereafter. Evans' findings are typical of the results obtained by many other investigators. Clearly, the importance of the "reinforcing dose" cannot possibly be overestimated. As stated by Christensen and Stilwell,[2d] the 6-to-12-month "reinforcing dose" should be regarded as an "integral and fundamental part of the original immunization procedure," and not as a "booster" dose in the usual sense.

Thus, there are three stages in adequate tetanus immunization: the first injections, the reinforcing dose, and subsequent booster doses. The first injections will be referred to in this report as "primary immunization," whereas the term "basic immunization" will be used to describe the complete basic procedure which comprises not only primary immunization but an appropriately timed reinforcing dose as well. This concept of adequate basic immunization is, of course, already well recognized in the scheduling of poliomyelitis vaccination and most pediatric immunizations. Moreover, the importance of the reinforcing dose has also been clearly demonstrated in diphtheria immunization.[14]

The discussion which follows will generally be in terms of the use of precipitated toxoid for routine immunization, unless otherwise specified.

Interval Between Basic Injections.—It has long been known that the interval between injections has an important influence on the antibody response. During the past 30 years a number of investigators have shown, specifically for toxoids, that such antigens lost much of their efficacy if they are given in doses less than about three weeks apart. Sachs[15] has shown that six weeks may be even better. The minimum interval at which the reinforcing dose will be effective is not so clearly defined, but it is well established that lengthening the interval generally increases the effectiveness of the injection. Thus, the time at which this dose should be given is not rigidly fixed and may depend, in part, upon the circumstances of handling the patient. If the patient were to be unavailable for injection at the usual interval of 10 to 12 months (e. g., because of travel), it is justified to give the reinforcing dose as early as 6 months after initiating immunization. In other words, there are no absolute fixed intervals at which injections of tetanus toxoid (or of any other antigen) must be given, but there are minimum intervals below which the desired effect may not be obtained and maximum intervals beyond which it may not be safe to wait for completion of immunization.

Response in Young Infants.—Immunization of young infants against tetanus normally presents no problem,[16] but, if done in combination, as with DPT, difficulty may arise in inducing satisfactory immune levels against diphtheria or pertussis, due to the well-established interfering effect of antibodies transferred passively from the mother through the placenta. This inhibition of antibody formation in very young infants can be largely, but perhaps not entirely, compensated for by the reinforcing dose given 6 to 12 months later.[17] However, to avoid this problem, many schedules advise postponing immunization of infants with DPT until three to six months after birth.

On the other hand, the prevention of neonatal tetanus can be approached through immunization of pregnant mothers living in areas where neonatal tetanus is not uncommon. This has indeed been advocated,[18] but it has also been warned against,[9] since it might interfere with effective neonatal antitetanus immunization. Nevertheless, it would appear immunologically sound to employ antenatal tetanus toxoid immunization in areas where neonatal tetanus is a serious problem and then to establish adequate tetanus immunity in the infants, either by postponing immunization until age three to six months or by giving an extra dose of the immunizating agent as part of the primary immunization schedule.

Competition of Antigens.—From animal experiments it has long been known that, under certain circumstances, when two or more antigens compete, as it were, for the response of the antibody-forming tissues, the stimulus induced by one antigen may be suppressed. Barr and Llewellyn-Jones[19] have more recently proposed the vivid term "crowding out" for this phenomenon. Only recently Chen and his associates[20] have demonstrated that this phenomenon can be observed in man. They showed that, in children with preexisting diphtheria immunity, primary immunization with DPT led to lower tetanus and pertussis antibody responses than were found in children without such preexisting immunity. However, a later paper by Chen and co-workers[21] indicated that, after a reinforcing dose at one year, antitoxin levels in the two groups became almost identical. Essentially similar findings were obtained by Wiener, Patterson, and MacKenzie.[22] Thus, to date, there is no clear-cut evidence that the problem which might be created by "crowding out" cannot be surmounted by currently accepted immunization schedules.

Duration of Effect of Primary Immunization.—As noted previously, custom dictated that the reinforcing dose is ordinarily given about one year after primary immunization, although it is permissible to give it as early as six months later. This implies the assumption that primary immunization will give the necessary degree of protection against unrecognized injuries for at least one year and that it will

maintain responsiveness to a subsequent reinforcing or emergency booster dose of toxoid for this period of time. It is of interest that about 10 percent of American soldiers[23] and a higher proportion of Canadian soldiers[24] in World War II had titers below 0.01 unit one year after primary immunization. Nevertheless, the extremely low incidence of tetanus in these two groups suggests that the protection achieved by the procedures then used was exceptionally high. Since that time, the potency of toxoids has markedly increased, and in four more recent studies[25] only one small group, who were given two doses of fluid toxoid six weeks apart, has shown a comparable proportion of subjects below 0.01 unit at the end of one year.[15] Thus, it is safe to conclude that primary immunization with currently available toxoids, in adequate doses (i. e., at least two doses of precipitated toxoid or three doses of fluid toxoid), will serve its purpose as previously defined. However, it should be clearly noted that, if emergency tetanus prophylaxis is indicated during the waiting period between primary immunization and the reinforcing dose, a booster should be given. If such an emergency dose is given before six months have elapsed, it should be counted as part of the primary immunization. If given after six months, it should be regarded as the reinforcing dose.

From time to time special circumstances will suggest to the physician that, in a particular patient, augmentation of the primary immunization schedule may be desired, for example, if a patient were to be unavailable for the scheduled reinforcing dose. In any such situation—indeed, whenever the physician recognizes the need of an extra immunological stimulus for his patient (e. g., as with neonatal immunization)—an additional injection in the primary immunization schedule will accomplish the desired result.

Maintenance of Tetanus Immunity—Routine Booster Dose.—With tetanus immunization—as with most immunization procedures—after basic immunization has been established, each subsequent injection of the antigen leads to a rapid rise in the antibody level, followed by a drop which at first is rapid but later becomes very gradual; hence, measureable antibody levels usually persist much longer than after primary immunization. Successive injections of tetanus toxoid or certain other antigens induce successively higher peak responses, higher residual antitoxin levels, and longer periods during which antibodies are detectable. Thus, just as the reinforcing dose augments the protection begun with primary immunization, the injection of suitably timed booster doses will further augment the level of immunity and greatly prolong its effect. Actually, the function of periodic booster injections is twofold. In the first place, they reestablish a high level of immunity which normally lasts for several years, thus protecting the patient against tetanus infections arising from trivial or ignored injuries. Secondly, they maintain the subject in a state of responsiveness to toxoid, so that if an emergency booster is subsequently indicated, the patient will react to it promptly and vigorously. Thus, the periodic booster dose not only greatly enhances protection against tetanus but it obviates the occasional necessity of depending on antitoxin for prophylaxis because of uncertainty regarding the patient's immunity status.

Frequency of Administration of Booster Dose.—There is as yet no basis for defining precisely the optimal interval between such booster inoculations. Some physicians have given them as frequently as every one or two years, but there is no clear immunological justification for such frequent injections. The American armed forces have adopted an interval of four years, which is apparently wholly satisfactory. Others have adopted or suggested five years or three years. The difference between three and five years appears to be immaterial; the main point is that some regular procedure should be adopted in order to insure that routine booster injections are not overlooked.

Several studies carried out during the past decade[26] indicate that the levels sustained after a booster, as well as the capacity to respond to a subsequent booster, are maintained for much longer intervals than was at first supposed. Bigler[25b] followed up 300 infants, for various intervals up to 10 years, who had been given two or more basic injections of diphtheria-tetanus toxoid. Every subject still had a measurable serum antitoxin level. Although high levels of antitoxin were less commonly found more than five years after the last dose of tetanus toxoid, many of these children retained high levels for as long as eight to nine years.

Similarly, in eight subjects observed by Regamey and Schlegel[26b] 10 years after basic inoculation with TABT, the lowest titer found was 0.075 unit. In 52 other subjects inoculated from one to nine years prior to the study, the lowest titer was 0.0075 unit. Looney, Edsall, Ipsen, and Chasen[11] studied a group of 144 veterans 1 to 10 years after their last inoculation of toxoid. Ten percent of these subjects were found to have antitoxin levels below 0.025 unit per milliliter. However, the frequency of low titers showed no relation to the interval since the last injection of toxoid. Similarly, Turner, Stafford, and Goldman[25c] titrated tetanus antitoxin levels in 145 subjects, mostly veterans. Half of them had received their last dose of toxoid from 5 to 11 years previously, whereas the other half had been injected less than 5 years before the study. The median antitoxin level in the former group was tenfold lower than that found in the more recently injected subjects. However, only six subjects in the longer-interval group and three in the shorter-interval group had fallen to less than 0.01 unit when tested.

Equally well-sustained levels were observed by Peterson and colleagues[26c] in 200 veterans tested up to 13 years after their last tetanus toxoid injection and by Moss and co-workers[10d] in 100 Canadian ex-service men. The latter group included three individuals in whom the interval since their last inoculation was 11, 13, 15 years. These three, incidentally, were the only ones in Moss' study whose titers had fallen below 0.01 unit. In the group studied by Peterson, 5 of 106 subjects observed seven or more years after their last injection had titers below 0.01 unit, whereas none of 41 subjects studied less than four years after their last toxoid injection were in this low range. Here again it appears that tetanus antitoxin levels will be sustained for a number of years after adequate basic immunization and a booster dose, with only a gradual fall in titer over the years.

This finding is not unique; similar results have been reported by Bojlen and Scheibel[14a] in children immunized against diphtheria with two primary doses of precipitated diphtheria toxoid and a reinforcing dose one year later. In these children the average antitoxin titers were essentially the same, whether the interval was three, six, or nine years after administration of the reinforcing dose.

These findings are consistent with the remarkable degree of clinical protection achieved in military personnel during World War II and in the Korean episode[10a] and with Ipsen's[8] finding that tetanus in civilian life has been markedly reduced since World War II among males in the veteran's age group. Thus, again it appears that the standard American and Canadian military practice is highly effective in preventing tetanus.

The data presented suggest the possibility that the interval between routine boosters might be lengthened to as much as 8 to 10 years. However, because there is a definite tendency for the antitoxin level to fall gradually[27] and also because data on titers at the longer intervals are relatively scanty, it would seem wise not to separate routine periodic boosters by more than four or five years.

Reaction to Tetanus Toxoid.—Annual booster injections of 0.1 cc. of toxoid given intradermally have been advocated[2f] as a method of insuring the maintenance of a "perennial state of immunity." Such a schedule has the advantage of regularity and convenience, although it has not been demonstrated that the "poor responder" will respond better to

this schedule than to larger doses given less frequently. On the other hand, there may well be contraindications to overfrequent immunization, since a small but growing number of unpublished observations indicate that rather marked delayed-type local reactions—basically not unlike those seen in individuals sensitive to diphtheria toxoid—have occurred in people receiving tetanus toxoid after numerous previous inoculations of this substance. It is not unlikely that the repeated inoculation of any antigen may, in a small proportion of subjects, induce a delayed-type hypersensitive state of the type known as "tuberculin allergy" or "delayed bacterial allergy" and similar to the reaction to the tuberculin test or the Moloney test. Furthermore, it appears probable that such sensitization is somewhat more likely to result from the intracutaneous route than from other routes of injection.[28] Therefore, it appears wise to avoid overimmunization and to give only as many inoculations of tetanus toxoid as are clearly justified. It is worth mentioning that the presence of delayed-type hypersensitivity in a patient cannot, in practice, be ascertained prior to injection of an emergency booster dose of tetanus toxoid, as has been suggested.[29] Not only has no such test been standardized sufficiently to provide a basis for its interpretation but the wait of 24 to 48 hours required for reading the test would preclude its use in an emergency.[30] If doubt exists as to a patient's tolerance for toxoid and if an emergency booster dose is indicated, a small dose (e. g., 0.05 to 0.1 cc.) may be given subcutaneously and the rest of the dose given 12 hours later if no reaction has occurred. If a marked reaction should ensue, further toxoid injections at that time may be safely omitted, since it has been shown years ago that reducing the dose of tetanus toxoid does not proportionately reduce the magnitude of the response obtained.[31]

It should be noted that the delayed-type reactions are totally different from the immediate, urticarial-type reactions, occasionally reported as following the injection of tetanus toxoid. Some reactions of the immediate type have been shown to be due to the trace contamination of the toxoid with unrelated substances.[32]

In general, however, reactions to tetanus toxoid are so extremely rare as to be almost insignificant. Aside from the occasional delayed-type reaction noted and the rare reaction to extraneous substances, there are doubtless a few—a very few—individuals with a true allergic sensitivity to the toxoid protein itself. If such patients are observed, it is to be hoped that thorough immunological studies on them will be reported.

Response to Booster Dose.—A number of the studies cited have recorded the degree and in some cases the rate of the response to a booster dose, given from 1 to 15 years after the last previous injection of toxoid.[26] In general, when titrations are done seven days or more after a booster injection, only a few individuals will exhibit titers below 0.1 unit, and levels below 0.01 unit will be extremely rare. For example, all of about 140 subjects tested by Bigler one to two weeks after a booster dose showed ample antitoxin levels.

Regamey and Schlegel[26b] observed good antibody responses in all of their 60 subjects at intervals from 1 to 10 years after their last inoculation; the minimum titer observed by them (six days after the booster injection) was 0.15 unit. All but one of the subjects studied by Looney and co-workers[11] and all of the subjects studied by Turner and co-workers,[25c] Peterson and co-workers,[26c] and Moss and colleagues[10d] showed a good response to the booster dose. Thus, it appears well established that a routine booster dose of toxoid, given as long as 15 years after the last injection of toxoid, will induce a rise in antibody level, except in the rare individual who cannot respond to an antigenic stimulus.

Rate of Response to Booster Inoculation.—The rate of response has been under study for many years. Recent studies have employed larger groups and, in many cases, better antigens than the earlier studies, so that they probably provide a sounder basis for answering the question. In three subjects studied by Bigler,[25b] the injection of precipitated toxoid was followed by a rise in antitoxin level beginning in three, four, and five days respectively. Among Regamey's and Schlegel's 60 subjects, the lowest titer observed four days after the booster was 0.035 unit. Turner and colleagues found 2 out of 48 subjects with a level below 0.01 unit and 8 below 0.1 unit four days after a fluid toxoid booster; however, all had risen to >0.01 (and all but 2 to >0.1) by the seventh day. In Looney's group,[11] four subjects showed levels below 0.025 unit six days after a booster dose of precipitated toxoid. Two of these showed excellent subsequent responses; one (as noted previously) showed essentially no response at all, and one could not be followed up. Peterson and co-workers tested titers six to seven days after the booster. At this time all 216 of their subjects had levels above 0.01 unit, and all but two were above 0.1. Ninety-four of Moss' subjects, when tested one week after a booster injection, had a level of over 0.1 unit of antitoxin.

Miller and colleagues[33] noted that the speed of response appeared to be somewhat slower in subjects whose basic immunization had occurred more than six years earlier. The four subjects observed by Looney, who failed to respond within six days, had all received their last inoculation five or more years previously. These scanty data suggest that the rate of response may be slower when the interval since boosting has been longer, and thus give further justification to the recommendation that routine booster inoculations be scheduled at intervals no longer than five years.

Thus, it appears that perhaps 95 percent of subjects receiving a booster injection will respond within four days, and about 100 percent within seven days, even when 10 or more years have elapsed since the last inoculation. The few exceptions appear to be predominantly among subjects who have not received toxoid for over five years.

Miller and colleagues[33] compared the effect of fluid toxoid and precipitated toxoid, with regard to the rate of response after a booster injection. They found that increases in antitoxin titer (levels not given) appeared within four to five days in 30 out of 33 subjects given a booster with fluid toxoid, but in only 15 out of 34 subjects given precipitated toxoid. These findings have provided the basis for the widespread recommendation that fluid toxoid be used for emergency booster injections rather than precipitated toxoid. The findings of Schlegel[34] are similar; 13 out of 15 subjects injected with a booster dose of fluid toxoid (given seven to nine years after basic immunization with combined tetanus toxoid and typhoid-paratyphoid vaccine) showed a rise in level four days later, in contrast to only 1 out of 12 receiving precipitated toxoid. The studies of Volk and co-workers[35] on diphtheria immunization appear to provide additional evidence for the assumption that the response to a fluid toxoid booster may be somewhat faster than that to a precipitated toxoid. On the other hand, Ipsen,[8] using identical Lf doses of toxoid in paired experiments, found that with either 1 Lf or 5 Lf, the antitoxin levels reached at one week were five to seven times higher after administration of precipitated toxoid than after giving fluid toxoid. Moreover, neither Miller nor Schlegel stated the Lf titers of the toxoids they employed, so that it is impossible to tell whether their groups were genuinely comparable. Thus, the choice between fluid toxoid and precipitated toxoid for the emergency booster is still not unequivocally decided.

Management of Patients with Tetanus-prone Injuries

General application of the immunization procedures just discussed would prevent practically all cases of tetanus which might otherwise follow trivial or unrecognized wounds. However, each recognized injury must be considered individually, and the handling of such injuries varies according to the circumstances subsequently discussed.

It cannot be emphasized too often that the most important procedure in the handling of tetanus-prone injuries, regardless of immunization history, is adequate cleansing and débridement of the injury. Clearly, tetanus can occur only when

susceptible tissue is infected with tetanus bacilli, and no history of immunization can eliminate the necessity of removing, insofar as possible, both the foreign material and the intruded epidermis which introduce tetanus infection and the necrotic tissue which nurtures it. The ubiquity in nature of the tetanus bacillus is not always fully recognized; it is independent of obvious "dirt."

As regards specific prophylaxis, various general recommendations have been outlined. Christensen[2e] advocates tetanus toxoid alone if the subject has an adequate history of toxoid immunization within five years. If over five years have elapsed, "particularly if the patient has a more serious injury such as a compound fracture, extensive burns, crushing injuries, gunshot or shrapnel wounds," he recommends giving tetanus toxoid and 1,500 units of antitoxin simultaneously at different sites. However, if the patient is sensitive to horse serum, he advises depending on toxoid alone. For the unimmunized subject who has sustained a tetanus-prone wound, Christensen advocates 1,500 to 3,000 antitoxin units, or more if indicated. He outlines in detail a procedure for testing patients for sensitivity to horse serum and for "desensitizing" positive patients with slowly increasing doses of antitoxin.

Parish, Laurent, and Moynihan[2j] itemize the types of injury that require tetanus prophylaxis. They list (1) wounds over three to four hours old; (2) definitely infected wounds; (3) wounds through skin probably contaminated by soil; (4) all deep and punctured wounds; (5) wounds with devitalized tissue, e. g., crushing injuries; and (6) wounds that cannot be closed properly. They cite the fairly rigid definitions of "actively immune" and "non-immune" patients adopted by the British army several years ago, but which I find unduly conservative in the light of current knowledge regarding the response to primary or basic immunization.

The definition of the "non-immune" subject is not simple. Unfortunately, it must include all those subjects in whom there is a vague history or suspicion of a history of tetanus toxoid immunization but no definite confirmation. It will, perforce, include those subjects who say they have been "immunized" to tetanus but cannot specifically show that what they had was tetanus toxoid immunization, rather than tetanus antitoxin, diphtheria toxoid, "typhoid," or some other inoculation readily confused with tetanus toxoid by the layman. It will include individuals who have only had one dose of toxoid, and it should probably include individuals who had only primary immunization (but no "third dose" or boosters) more than five years previous to the injury in question. Finally, there is, of course, a large group of individuals who have clearly not had any tetanus toxoid inoculations. Thus, tetanus-prone injuries may be sorted into three categories, depending on whether they occur in a well-immunized individual, in an individual with waning or latent immunity, or in a patient with an inadequate, unreliable, or negative history of immunization against tetanus.

Clearly, the effective use of tetanus toxoid in the emergency prophylaxis of tetanus is dependent not only on adequate prior immunization but also on available and reliable evidence that this has been actually carried out. It is universally recognized and advocated[2f] that veterans of military service may be regarded as having had tetanus immunization and may be handled accordingly. Over and above this, definite knowledge regarding a patient's immunity status is usually limited to a physician's own records. This is a deplorable situation and can only be remedied by a sustained, united effort on the part of the medical and public health professions.

It would be desirable for all immunized persons to carry with them a record of their tetanus toxoid injections; even though such records may get lost or may not be kept up to date, it is obviously better to have such records available frequently than not to have them at all. Parish[36] has recently stated the case for this practice lucidly and cogently and has advocated the use of metal disks for this purpose. To supplement such records, a central community file could be set up, maintained by the county medical society or by the health department.[2g] When such personnel and central file records become generally available, much of the uncertainty which now clouds the handling of tetanus-prone injuries will be eliminated.

Handling of Immunized Patient.—From the data cited, it would appear that an individual with a history of properly performed primary tetanus immunization, administered within the previous five years, is virtually certain to show an ample response to an emergency or "wound" booster dose, beginning within five days after the booster injection. For such patients, a booster dose of toxoid should provide ample immunological protection against tetanus if it is given within 24 hours, regardless of the type of injury. If serious delay has occurred in giving toxoid and if the injuries are such that fulminating tetanus might be expected, then the physician may, in individual cases, weigh the advisability of giving 1,500 units of antitoxin at the same time, at a separate site. (Since 1950 the American unit and the International unit have been identical. Prior to this date an International unit contained one-half as much antitoxin as an American unit.)

When the interval since the last dose of toxoid has been more than 5 years and less than 10 years and when the patient has a clear-cut history of adequate basic immunization, an emergency booster dose of toxoid will be sufficient prophylaxis for ordinary injuries treated promptly. However, if delay has occurred in administering toxoid and if the risk of tetanus is self-evident (e. g., gunshot wounds, compound fractures, dirty wounds difficult to débride and expose), there is some theoretical justification for giving a simultaneous injection of 1,500 units of antitoxin. Even when more than 10 years have elapsed since the last dose of toxoid, prompt administration of a booster dose of tetanus toxoid will suffice to protect the patient in the vast majority of instances. Nevertheless, here the physician's judgment is paramount, and in such patients the procedure of giving a booster dose of toxoid simultaneously with 1,500 units of tetanus antitoxin is a justifiable, though conservative, method of providing additional prophylaxis in the presence of clearly tetanus-prone injuries. It must be weighed, however, against the likelihood of unfavorable reactions to the antitoxin.

Interval Between Emergency Booster Doses.—Frequently a patient is seen with a tetanus-prone injury, a few months after a known, recorded, previous booster dose of tetanus toxoid, and the thoughtful physician will naturally ask himself whether another booster dose is needed. Parish and colleagues[2j] have recommended that a booster dose which was given within the preceding 18 months renders another booster dose unnecessary. Others have set up a 12-month limit,[37] a limit of "a year, and possibly several years,"[38] or a three-year limit.[26c] The available data do not provide a basis for an absolute rule on this question, but, in view of the extensive evidence[26] that protective antitoxin levels persist in a vast majority of subjects for much longer than a year, I would recommend a one-year interval of freedom from repeat booster injections except in patients in whom massive tetanus infection appears to be a definite hazard.

Effectiveness of Combined Active-Passive Immunization in Previously Immunized Persons.—Simultaneous administration of toxoid and antitoxin has been suggested previously as a method of handling certain situations in which genuine, serious doubt arises regarding the adequacy of a toxoid booster dose alone. This practice appears to be immunologically sound. Miller, Ryan and Beard[39] demonstrated the efficacy of such a procedure in rabbits. They then gave 1,500 units of tetanus antitoxin and a booster dose of tetanus toxoid, simultaneously but in a separate site, to four patients previously immunized with toxoid.[39a] Three of their subjects showed vigorous antitoxin responses by the fourth or fifth day; the fourth subject showed essentially no response, and the authors believed that this subject was immunologically a poor responder. A larger group of 23 subjects was studied by Sachs[15] who gave 1 cc. of fluid tetanus toxoid

and 500 units of antitoxin in opposite arms of the patient at the same time. By the 9th and 12th day, all subjects had titers from 1 to 100 units.

Thus, in certain selected previously immunized subjects, simultaneous active and passive immunization, achieved by injecting 1,500 units of antitoxin and (at a separate site) a routine booster dose of toxoid, provides a needed combination of immediate and long-term protection against tetanus. This procedure tides the patient over the period of uncertain protection during the first few days in those with waning immunity, potentially fulminating infection, or serious delay in administering toxoid. It should be borne in mind that the booster effect of the toxoid might well be blanketed if more than 1,500 units of antitoxin were given. Moreover, there is no immunological justification for larger doses of prophylactic antitoxin in such patients.

Tetanus Prophylaxis in Unimmunized Patients.—For unimmunized patients, the classic procedure, standardized toward the end of World War I, has been to administer 1,500 units of tetanus antitoxin as soon as the patient with a tetanus-prone injury has been evaluated for sensitivity to horse serum. Space does not permit a detailed discussion of the controversial views which are at hand regarding what constitutes an adequate basis for determining a patient's sensitivity to horse serum. The usual practice is to perform intradermal or conjunctival tests, or both, with epinephrine immediately at hand in the event of an untoward reaction.[2e]

On the other hand, Laurent and Parish[40] maintain that neither the intradermal nor the conjunctival test is reliable, both false-positive and false-negative reactions having been seen with both tests. They quite properly point out that a carefully elicited history of allergic conditions or previous serum injections is of paramount importance, and they would replace "sensitivity tests" with a small subcutaneous trial dose in persons with histories suggesting allergy. Their proposal to discontinue skin and eye tests will not be readily accepted unless more evidence is accumulated that such tests are misleading; however, the "trial dose" concept—if employed with great caution—would appear to deserve further study.

If it is not possible to débride the injury adequately, it has been customary to administer successive 1,500-unit doses of antitoxin at intervals of one to two weeks two or three times or until the wound has healed. It is undoubtedly true that this procedure contributed to the remarkably low incidence of about 1 case per 7,700 wounds or injuries in the United States army during World War I. Between World Wars I and II, the rate dropped further to 1 case per 40,000 wounds and injuries. This is really a remarkable record but is, nevertheless, short of the ideal of the practicing physician.

One suspects that the incidence of failure may be higher in civilian life. Certainly, there are numerous recorded instances in which the prompt injection of 1,500 units of antitoxin has failed to prevent tetanus. Hence, many physicians such as Martini[4] and Spaeth[2f] recommended giving 10,000 or more units of prophylactic antitoxin routinely in all cases in which its use is indicated. Others[2e] have suggested a range of 1,500 to 30,000 units depending on the circumstances, whereas many others[2h] stand by the classic dose of 1,500 units. Stotzer[21] suggests that "rather than following a rigid standard (in employing 1,500 units of antitoxin routinely) it would seem better to use this as a minimum dose and adjust the dosage to the patient's need." Stafford[2h] would omit antitoxin entirely in subjects who are sensitive to horse serum. He recommends keeping such patients under close observation and starting tetanus toxoid injections immediately.

Thus, there is no general agreement regarding the dose of antitoxin to employ in the prophylaxis of tetanus in the unimmunized individual. Indeed, there are those[41] who appear to doubt that the usual dose of prophylactic tetanus antitoxin is efficacious at all. This nihilistic view is unjustified, and genuine evidence to support it is not presented. The observation cited by Stafford that, in Baltimore, tetanus has occurred just as often in patients given antitoxin prophylaxis as in those not so treated is actually uninterpretable, since there is no information on the proportion or the severity of injuries for which antitoxin was given. Furthermore, aside from the World War I experience,[15] there is ample experimental evidence, dating back many years, that antitoxin prophylaxis can prevent the occurrence of tetanus in experimentally infected animals.

Assuming that prophylactic antitoxin is indicated in a given situation, what dose will provide virtually certain protection, without unduly increasing the incidence of serum sickness and the risk of other serum reactions? This question cannot be answered on the basis of experience in man. In any case, the answer will vary with the type of injury, the feasibility of adequate débridement, the interval since injury, and the immunological status of the patient with respect to horse serum. Thus, it is impossible to predict correctly the patient in whom 1,500 units of antitoxin will fail to give protection. Therefore, when the administration of antitoxin is clearly indicated, it is logical to advocate larger doses as a routine measure. Increasing the dose of antitoxin given to a normal patient will somewhat accelerate the appearance of antitoxin in the circulation and will increase the duration of the protection, so that the risk of fulminating tetanus or late tetanus—the two most likely causes of failure to protect with a small dose of antitoxin—will be diminished.

On the other hand, in a patient who possesses antibodies against horse serum (the type of person who characteristically manifests accelerated serum sickness), an increase in the dose of antitoxin given may not materially prolong its effectiveness. Confirming the classic observations of von Pirquet and Schick and of Rackemann and Longcope, Mahoney and Moloney[42] have shown that, in general, tetanus antitoxin disappeared from the circulation more rapidly in patients who had serum sickness than in those who did not exhibit this complication. Nevertheless, as a general rule, an increase in the dose of prophylactic antitoxin is definitely indicated if there has been delay in treating the wound, if the injury is difficult to débride and decontaminate, or if there is massive contamination of necrotic tissue. In such cases, the prophylactic administration of penicillin may be of some value. However, it must be remembered that penicillin is no substitute for specific prophylaxis and adequate débridement of the injury. The final decision must be made by the physician, who must balance his estimate of the risk of tetanus in the patient against the immediate, as well as the possible ultimate, consequences of administering antitoxin.

Since failures to protect a patient with 1,500 units of antitoxin have been recognized for over 40 years, why was not the recommended prophylactic dose increased long ago? The answer probably lies in the fear of serum reactions, not merely serum sickness, which is well known to increase in frequency with larger doses of serum, but also the danger of more serious complications such as neuritis, myelitis, periarteritis nodosa, deafness, pericarditis, myocarditis, encephalopathy, or fatal anaphylactic shock. However, the very general adoption of enzyme-purification methods has led during the past 20 years to the production of antitoxin of greater purity and a lower incidence of serum sickness than formerly.[43] With such improved methods available, there should be less hesitation in giving as much antitoxin as the physician's judgment of the tetanus hazard indicates. Nevertheless, the limitations in the effectiveness of increasing the dose and the hazards that accompany the administration of serum should always be borne in mind.

In my opinion, when prophylactic tetanus antitoxin is medically indicated, 3,000 to 5,000 units should be an adequate dose in patients over 10 years of age if seen on the day of injury, except in the case of compound fractures, gunshot wounds, or other wounds not readily débrided. Delay of more than one day or the presence of complications such as those would indicate a dose of 6,000 to 10,000 units or

more, depending on the circumstances of the individual case. Half of the stated dose should suffice in children under 10 years of age.

Active-Passive Immunization in the Unimmunized Subject.—The physician who is obligated to administer tetanus antitoxin to a patient because active immunization was never instituted will naturally want to obviate such an event occurring in the future, especially since reinjection of antitoxin is not only more likely to cause an untoward reaction but is likely to be more transient in its effect. Thus, it is logical to institute active immunization in patients who have received prophylactic antitoxin.

It has often been advocated that such patients be given tetanus toxoid at the same time as antitoxin, thus starting the patient on a course of immunization which, once having begun, he is presumably more than likely to finish. This procedure was recommended over 30 years ago by Ramon and has been employed for the control of both tetanus and diphtheria. The data on its effectiveness as regards tetanus are not explicitly clear. There have been several studies on this point in animals but few in man. Gold and Bachers[44] reported that the simultaneous administration of alum-precipitated tetanus toxoid to individuals given 1,500 units of antitoxin, followed by a second dose of toxoid two to three months later, led to a normal and adequate immune response in these individuals. When fluid toxoid was employed, three doses were essential to elicit a satisfactory antitoxin level. On the other hand, Huber[45] found that, with two doses of precipitated toxoid given 18 days apart, the response was not fully satisfactory when the first dose was given simultaneously with 1,500 units of prophylactic antitoxin. Hence, a third dose given sometime later was indicated if active immunization was to be successfully instituted. Thus, although it is possible to institute simultaneous active-passive immunization with precipitated toxoid and 1,500 units of antitoxin, the results do not appear to be as reliable as those obtained with toxoid alone. Stated differently, these studies suggest that, if active-passive immunization is employed, three doses of toxoid should be given in order to achieve satisfactory results. Moreover, if large doses of antitoxin are administered, simultaneous active-passive immunization is apparently impractical,[46] and initiation of active immunization must definitely be delayed for several weeks; the waiting period depends on the amount of antitoxin given. In other words, the procedure of active-passive primary immunization may be employed when psychological or other circumstances warrant it, but it cannot be definitely relied upon unless no more than 1,500 to 3,000 units of antitoxin are given, and unless three doses of toxoid are included in the basic schedule. Fluid toxoid appears to be less efficient for this purpose.[47]

Summary

Active and Passive Immunization.—Passive immunization against tetanus provides immediate but transient protection against tetanus. In contrast, active immunization with toxoid leads to a slowly developing but long-lasting immunity. Passive immunization has numerous disadvantages and has never, at its best, given as high a degree of protection as does active immunization. Hence the latter is the procedure of choice for the specific prophylaxis of tetanus, whenever time and circumstance permit it to be applied.

Use and Effectiveness of Tetanus Toxoid in Routine Immunization.—Tetanus toxoid is one of the most effective and innocuous immunizing agents known. Since all human beings are subject to some chance of contracting tetanus, all people should, ideally, be immunized with toxoid. In particular, high-risk groups and groups readily reached en masse should have such immunization as a matter of routine medical and health policy. Adequate immunization against tetanus may be achieved with a variety of separate or combined preparations. It is important to administer at least three doses of fluid toxoid or two doses of precipitated toxoid in order to establish acceptable primary immunization. "Basic immunization" may not be regarded as completed until an additional reinforcing dose is given, preferably 6 to 12 months after primary immunization. This reinforcing dose greatly enhances and prolongs the immunity established with primary immunization. Immunization of infants is readily accomplished, but, if the infant is born of an immunized mother, an extra dose of toxoid (or the appropriate combined vaccine) is recommended as part of the primary immunization. Such an extra dose is also recommended whenever there is specific indication for early achievement of a high and lasting level of immunity.

Immunity to tetanus, once established by adequate basic immunization, should be maintained at a protective level by periodic booster doses. The level of immunity falls, though very slowly, for years after basic immunization or reimmunization. Hence, it appears wise to administer booster injections at intervals of four to five years. Shorter intervals are not ordinarily indicated, especially since there is some evidence that repeated inoculations may lead to sensitization of the delayed type in a small proportion of patients. Longer intervals—up to 10 years or more—do not appear to decrease the capacity of the booster dose to elicit a response, but the rate of response may perhaps be somewhat slower.

A detectable rise in antitoxin level after a booster injection occurs in almost all subjects within five days and sometimes sooner. There is some evidence, though not unanimous agreement, that fluid toxoid elicits a slightly more rapid response than does precipitated toxoid.

Management of Patients with Tetanus-prone Injuries.—The prevention of tetanus after an injury is dependent first upon adequate surgical care of the injury, with emphasis upon débridement and exposure of the injured area and removal of foreign material. Specific prophylaxis with tetanus toxoid will be of incontestable value if the patient has a known reliable history of primary immunization within five years or of primary immunization plus reinforcing or booster doses at any time. Prompt injection of tetanus toxoid in such patients will give adequate protection against tetanus in practically all cases. However, simultaneous injection of 1,500 units of antitoxin, at a different site, may be considered for patients with clearly tetanus-prone injuries under conditions of exceptional risk, such as a delay of more than 24 hours in treating a massively contaminated or deeply penetrating injury, an interval of over 10 years since the last injection of toxoid, or, in intermediate situations, a combination of delay in treatment and severity of injury. The combined use of toxoid and antitoxin, in those few situations in which it is indicated, will minimize the risk of fulminating tetanus during the interval prior to the appearance of the booster response to tetanus toxiod. This advantage is to be balanced against the hazard or inconvenience of a possible reaction to the antitoxin.

The long persistence of protective residual antitoxin titers after a booster dose will serve to prevent many cases of tetanus arising from trivial or unrecognized injuries and will render unnecessary the repetition of successive emergency booster injections of toxoid at close intervals, except when the risk of massive tetanus infection is apparent.

In patients without a valid history of adequate tetanus toxoid immunization, tetanus antitoxin must be employed for emergency prophylaxis of tetanus-prone injuries. The customary dose of 1,500 units does not give entirely reliable protection, and a dose of 3,000 to 5,000 units is recommended when prophylaxis of tetanus is medically indicated. This dose should be increased if complete débridement is impractical or if significant delay has occurred in treating the injury.

The unimmunized subject should be immunized as soon as practical. It is possible to begin active immunization at the same time as prophylactic antitoxin is given, but the procedure is effective only if the dose of antitoxin is relatively small and if an extra dose of toxoid is included in the primary immunization schedule. Precipitated toxoid is preferable to fluid toxoid for this purpose.

Because of space limitation the references will be published in the author's reprints only.

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POSITIONS

in hospital pharmacy

. . . . . .

The Personnel Placement Service is operated without charge for the benefit of hospitals and pharmacist members of the American Pharmaceutical Association and the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS. The ultimate purpose is the improvement of pharmaceutical services in hospitals, by more adequately fulfilling hospital pharmacy personnel needs and by locating positions which provide challenging opportunities for pharmacists who have indicated an interest in a hospital career.

By participating in the service, the hospital indicates a desire to achieve a pharmaceutical service which meets the Minimum Standard for Pharmacies in Hospitals. A description of the position should be submitted to the Division of Hospital Pharmacy on the forms provided. The hospital will receive applications directly from the applicant. The hospital agrees to reply to each application received and to notify the Division of Hospital Pharmacy when the position is filled.

The pharmacist, by participating, agrees to submit a Personnel Placement Service Information Form to the Division of Hospital Pharmacy. The applicant will then be notified of openings listed with the Service as they become available and can negotiate directly with the hospital if he is interested. It is agreed that the Division of Hospital Pharmacy will be notified as soon as a position is accepted.

A listing of positions open and wanted will be made regularly in the AMERICAN JOURNAL OF HOSPITAL PHARMACY without charge. Neither the name of the hospital offering the position nor the name of the applicant will be listed, except by code. All inquiries should be directed as shown below, including the code number.

Address all inquiries to
Division of Hospital Pharmacy
2215 Constitution Avenue, N. W.
Washington 7, D.C.

positions open

ASSISTANT CHIEF PHARMACIST—300 bed hospital located in Pennsylvania. Duties include prescription dispensing and compounding, manufacturing, narcotic inventory control, and maintaining stock preparations. Prefer young man. PO-175

ASSISTANT CHIEF AND/OR STAFF PHARMACIST—330 bed voluntary general hospital located in the Midwest. Duties include compounding and dispensing medications to inpatients, outpatients, and employees. PO-174

STAFF PHARMACIST—Outstanding opportunity in large, well-known hospital located in the Midwest. Duties include filling prescriptions and floor supply, and some bulk compounding. Eligible for registration in Minnesota; hospital experience preferred. PO-173

PHARMACIST—60 bed hospital located in southwest Colorado needs services of a competent pharmacist. Generous benefits include meals while on duty. Male or female. Excellent quarters available to a single female at very nominal fee in new nurse residency. PO-172

PHARMACIST—800 bed general hospital. Compounds and dispenses medications, sells proprietary medicines, sundries and allied supplies to both in and outpatients. Must be licensed in Indiana or eligible for licensure. Fifty hour week, 2 weeks vacation after 1 year, 3 weeks after 3 years and 4 weeks after 5 years, retirement program entirely free, liberal employee discounts. PO-171

STAFF PHARMACIST—290 bed general medical and surgical city hospital. Duties include compounding, dispensing, manufacturing, and assisting in the purchasing of supplies. Prepares reports and maintains records. Furnishes information concerning medications to physicians and nurses. In absence of associate pharmacist will assist with special duties as assigned by chief pharmacist. Male or female between 23-45 years of age. Ohio registration required. Hospital pharmacy internship preferred. Forty hour week, 2-3 weeks vacation, 15 day sick leave, retirement plan, credit union, 6 holidays, Blue Cross available. PO-170

STAFF PHARMACIST—200 bed general hospital. Duties include compounding, dispensing and manufacturing. Applicant must have B. S. in Pharmacy and registered in Conn. Recent graduate acceptable. Forty-four hours per week, two weeks' vacation, pension plan and hospitalization. PO-168

ASST. CHIEF PHARMACIST—102 bed general hospital located in Oregon. Pleasant surroundings in college city of 8,000-20,000 students. Male or female. Must be registered. Forty hour week, 2 weeks' vacation, holidays and sick days. PO-166

ASSISTANT CHIEF PHARMACIST—350 bed general hospital. Assist in training and supervision of employees and in plans and projects of dept. Direct dept. in absence of chief pharmacist. Registration in Ohio and B.S. degree required. Only male considered, must be over 21 years of age. Forty hour week, 2 weeks vacation, Social Security, paid holidays, group hospitalization, sick leave. PO-165

STAFF PHARMACIST—100 bed general hospital located in Texas. Assume personal responsibility for accurate filling of prescriptions and supplies, assist in inspecting drugs in nursing stations, replace stock taken from night emergency container, inspect and refill ophthalmic solution trays from operating room, emergency room and central supply. Female preferred. Must be registered or eligible for registration in Texas. Forty hour week, 2 weeks vacation after one year, paid holidays, 7 days sick leave. PO-164

ASST. CHIEF PHARMACIST—280 bed general hospital. Duties include filling prescriptions and medicine orders from various units, supervise pharmacy clerks, assume administrative responsibility when chief pharmacist is absent. Forty-four hour week, sick leave and six paid holidays. Must be registered in Ill. PO-161

ASST. CHIEF PHARMACIST—293 bed general hospital. Dispensing drugs to nursing stations, filling special orders for patients, ordering stock, keeping records and some manufacturing. Forty hour week, 2 weeks' vacation, 12 days sick leave, 6 holidays, meals while on duty, free hospital care. Must be registered in Md. PO-160

ASST. CHIEF PHARMACIST—235 bed general hospital located 7 miles from Akron, Ohio. Hospital expanding to 310 beds in 1960, pharmacy expanding to serve 500 beds. Filling prescriptions, small volume of manufacturing. Must assume responsibility for pharmacy in the absence of chief pharmacist. Forty hour week, 2 weeks' vacation, hospital insurance paid for employee after 6 months probationary period, paid sick leave, 6 paid holidays. PO-159

CHIEF PHARMACIST—103 bed general hospital. Purchasing, receiving and issuing of pharmacy supplies. Taking inventory once a year. Filling out various reports necessary to operation of dept., etc. Must be registered in Wash. State. Forty hours per week, 2 weeks' vacation, 7 paid holidays, 1 sick day per month cumulative to 48, Blue Cross Insurance available. PO-158

STAFF PHARMACIST—269 bed nonprofit general hospital located in Calif. Duties include filling ward orders, individual prescriptions, outpatient prescriptions and narcotic orders. Applicant must have B.S. in pharmacy, 1 year's experience or preferably hospital pharmacy internship. Willingness to work week ends and nights as required. Male or female. Forty to forty-eight hour week, two weeks' vacation after one year, 6 paid holidays, 12 days sick leave, hospital insurance plan. PO-157

CHIEF PHARMACIST—190 bed general hospital located in Wis. Pharmacist will have complete control of the pharmacy, responsible for dispensing, charges, inventory and purchasing. Work with Medical Staff to formulate policies for dept. with administrative approval. Capable of cooperating with the Medical Staff, helping the Medical Staff keep abreast of advances in the field, and guiding and directing the Nursing Staff in their usage of drugs. Thirty-six to forty-four hour week, two weeks' vacation after one year, Municipal Pension Plan, insurance, 10 days sick leave per year accumulative to 30. Must be registered in Wis. PO-156

SUPERVISOR OUTPATIENT PHARMACY OR STAFF PHARMACIST—236 open bed general state hospital located in Ark. Supervisor's duties include some teaching of pharmacy students, supervise one other pharmacy and administer this subdivision which fills

about 200 prescriptions daily. Must be an especially intelligent and well trained pharmacist preferably with an internship in hospital pharmacy. STAFF PHARMACIST rotates among the various subdivisions of the hospital pharmacy: outpatient pharmacy, inpatient pharmacy, non sterile manufacturing and sterile manufacturing. Should be a good pharmacist, intelligent, interested in hospital pharmacy professionally. Forty hour week, vacation, 6 paid holidays per year, opportunity to learn in one of the most active hospital pharmacy depts. in the country, after 2 years participate in retirement program which provides essentially a 6% increase in salary, close relationships with schools of pharmacy, medicine and nursing. PO-154

STAFF PHARMACIST—215 bed general hospital. Compound and dispense drugs, manufacture pharmaceuticals and assist in all other pharmaceutical duties in the pharmacy. B. S. required. Must be eligible for licensure in Pa. Forty hour week, three weeks' vacation, 7 holidays, 10 days paid sick leave, annual physical examinations, merit salary increases. PO-152

ASST. PHARMACIST—250 bed general hospital. Forty hour week, 2 weeks' vacation, sick leave and 6 paid holidays per year. Must be registered in N. C. PO-150

STAFF PHARMACISTS—Unique, new 400 bed general private hospital where pharmacists join the doctor-nurse team by working in a dispensing unit located on each 100 bed nursing unit or in the central pharmacy. The dispensing unit personnel have responsibility for providing drugs, oxygen, dressing trays, I. V. solutions and similar items. A total of sixteen staff pharmacists is required to staff the hospital. Applicants must be eligible for registration in Calif. Excellent opportunity; generous benefits. PO-148

ASST. CHIEF PHARMACIST—250 bed general hospital located in N. Y. Male preferred. Registration in N. Y. required. Ability to pass N. Y. State Civil Service examination. Duties include filling ward orders, patient prescriptions, checking stock and small volume parenteral solutions manufacturing. Forty hour week, 3 weeks' vacation, annual sick leave, 7 paid holidays, retirement plan, group insurance available. Located outside city. Some housing available on premises. PO-146

CHIEF PHARMACIST—150 bed general hospital located in N. M. To assume complete charge of purchasing and distributing drugs. PO-134

STAFF PHARMACIST—75 bed general, private hospital located in Ind. State registration required. Male or female. PO-131

CHIEF PHARMACIST—185 bed private nonprofit hospital located in Va. Prefer applicant with hospital pharmacy internship and one year's experience. PO-126

CHIEF PHARMACIST—60 bed mission hospital operated by Presbyterian National Missions; extensive outpatient dept.; on Navajo Indian Reservation near Gallup, N. M. Qualified to register in Ariz.; single man or woman, challenged by service rather than benefits. PO-122

STAFF PHARMACIST—150 bed general hospital. Only female considered. Must be eligible for Ill. registration. Forty hour week, 2 weeks' vacation. PO-116

ASST. CHIEF PHARMACIST—425 bed general hospital. Duties include dispensing and supervision of special projects. Prefer male applicant with internship in hospital pharmacy. Unique opportunity to obtain experience. PO-115

STAFF PHARMACIST—215 bed general hospital expanding to 35 more beds. N. Y. registration required as well as hospital experience. Forty hour week, 2 weeks' vacation. PO-104

ASST. CHIEF PHARMACIST—152 bed general hospital expanding to 180 beds. Registration in Neb. required. Forty hour week, 2 weeks' vacation. PO-101

CHIEF PHARMACIST—400 bed hospital located in the Midwest. Complete responsibility for the pharmaceutical of a normal modern hospital including drug purchasing and departmental staffing. Staff presently consists chief pharmacist, five staff pharmacists, clerk-typist, stock man, and several part-time workers. Salary to be based upon training and experience. PO-99

STAFF PHARMACIST—500 bed general hospital located in Okla. B. S. required. Forty hour week. PO-95

ASST. CHIEF PHARMACIST—315 bed general hospital. Registration in Iowa required. Experience desirable. Forty hour week, 2 weeks' vacation. PO-92

ASST. CHIEF PHARMACIST—237 bed general hospital in West Va. Female desired. Forty-four hour week, 2 weeks' vacation. PO-77

STAFF PHARMACIST—335 bed hospital located in Fla. Duties include responsibilities in outpatient dept. and parenteral solution room. Forty hour week, 2 weeks' vacation. One meal daily. PO-75

CHIEF PHARMACIST—88 bed hospital located in Pa. Planning expansion to 125 beds for general patients and 40 beds for chronic patients. Possibility for pharmacist to serve as Asst. Adm. in charge of Purchasing, Central Supply, and Store Room. Forty hour week, 2-4 weeks' vacation. Young man preferred. PO-59

ASST. CHIEF PHARMACIST—Large voluntary hospital located in Brooklyn. Must be eligible for registration in N. Y. Supervisory ability needed. Thirty-five hour week, 2 weeks' vacation, 10 days sick leave, 9 holidays. PO-51

positions wanted

CHIEF PHARMACIST—Male, single. B. S. received in 1952 at Mass. College of Pharmacy. Seven years' hospital pharmacy experience. Registered in Mass. Will locate anywhere. PW-218

STAFF OR CHIEF PHARMACIST—Male, single. B.S. received in 1952 at St. Louis College of Pharmacy. Two years' hospital pharmacy experience. Registered in Mo. Prefers West Coast, particularly Calif. PW-217

ASST. CHIEF OR STAFF PHARMACIST—Female, single. B. S. received at University of Saskatchewan in 1954. Three years' hospital pharmacy experience. Registered in Canada. Would prefer to locate in Southeastern or Western part of U. S. PW-216

CHIEF PHARMACIST—Male, married. Will receive M. S. in June, 1960 at the State University of Iowa. Served hospital pharmacy internship. Registered in Iowa, prefers to locate in the northern Middlewest. PW-215

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. B. S. received in 1954 at the Southwestern State College in Okla. Served hospital pharmacy internship at Springfield City Hospital, Springfield, Ohio. Three years' hospital pharmacy experience. Registered in Okla., prefers to locate in Southwest. PW-214

ASST. CHIEF OR STAFF PHARMACIST—Male, married. B. S. received in 1954 at the University of Ga. Three years' hospital pharmacy experience. Registered in Ga. Prefers South. PW-213

CHIEF PHARMACIST—Female, single. B. S. Eleven years' hospital pharmacy experience. Prefers N. Y. Registered in N. Y. PW-212

CHIEF PHARMACIST—Male, married. Ph.G. and B.S. from Temple University. Prefers to locate in N. J. or Pa.; registered in both states. PW-211

CHIEF PHARMACIST—Male, married. M. S. received from Philadelphia College of Pharmacy and Science in 1958. Served hospital pharmacy internship. Four years' hospital pharmacy experience. Presently completing military obligations. Will locate anywhere and will be available after July, 1960. Registered in Ohio. PW-210

ASST. CHIEF OR STAFF PHARMACIST—Female, single. B. S. Nineteen years' hospital pharmacy experience. Registered in Idaho, Alaska, Ohio, and Oregon. Prefers Seattle, Wash. or Northwest section of country. PW-209

ASST. OR STAFF PHARMACIST—Female, single. Received B. S. from Texas Southern University in 1958. One year hospital pharmacy experience. Registered in Texas and Utah. Prefers West and East. PW-208

CHIEF PHARMACIST—Male, married. Received B. S. in 1957 from Brooklyn College of Pharmacy. Over one year hospital pharmacy experience. Registered in N. Y. and Ill. Prefers East. PW-207

ASST. CHIEF PHARMACIST—Male, single. B. S. received in 1956 from Columbia University College of Pharmacy. Served hospital pharmacy internship. Two years' hospital pharmacy experience. Registered in N. Y. Prefers New York City. PW-206

DIRECTOR OF PHARMACY SERVICE AND/OR CHIEF PHARMACIST—Male, married. Served hospital pharmacy internship and received M. S. in Hospital Pharmacy from the University of Mich. in June, 1959. Seven years' pharmacy experience. Registered in Ill. and Mich. Will locate anywhere. PW-205

CHIEF PHARMACIST—Male, married. M. S. received from Philadelphia College of Pharmacy and Science in 1957. Served hospital pharmacy internship. Over four years' hospital pharmacy experience. Registered in Nebr., Ky., Iowa, and Pa. Prefers Midwest. PW-204

CHIEF PHARMACIST—Male, married. B. S. received from R. I. College of Pharmacy in 1953. Served hospital pharmacy internship from 1953-1955 at Jefferson Medical College Hospital. Four years' hospital pharmacy experience. Registered in Mass., R. I., Pa., and N. J. Prefers East. PW-203

ASST. CHIEF OR CHIEF PHARMACIST—Male, single. B. S. received from St. Louis College of Pharmacy in 1946. Fifteen years' hospital pharmacy experience. Registered in Mo. and S. C. Prefers Southeast section of country. PW-202

CHIEF PHARMACIST—Male, married. Served internship. Over three years' hospital pharmacy experience. Registered in Ohio and Pa. Prefers South. PW-201

STAFF OR ASST. CHIEF PHARMACIST—Male, single. B. S. degree received from Duquesne University, Pittsburgh in 1959. Served two years' internship in hospital pharmacy. Registered in Pa. Will locate anywhere in U. S. PW-200

STAFF PHARMACIST—Female, single. B. S. Seven years' hospital pharmacy experience. Southwest section of country preferred. Registered in Ala. and Ga. PW-199

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. B. S. received in 1952. One year's hospital pharmacy experience. Prefers Southeast section of country. Registered in Va. PW-198

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. B. S. received from Philadelphia College of Pharmacy and Science, 1956. Two and one-half years' hospital pharmacy experience and six years' experience in manufacturing, mainly parenterals. Presently working in Nicaragua. Will locate anywhere in U. S. PW-197

PHARMACIST—Male, single. Hospital pharmacy experience. B. S. Registered in Mo. and Ill. Will locate anywhere. PW-196

CHIEF PHARMACIST—Male, married. B. S. received in 1953. Four years' hospital pharmacy experience. Prefers Eastern part of country. Registered in Pa. and N. Y. PW-195

STAFF PHARMACIST—Female, single. B. S. Hospital pharmacy experience. Prefers central southern part of Canada. Registered in Philippines. PW-194

CHIEF PHARMACIST—Male, married. B. S. Ten years' hospital pharmacy experience. Registered in Pa., N. Y. and Fla. Prefer to locate in Pa. and N. Y. PW-193

CHIEF PHARMACIST—Male, single. A. B. degree received in 1949. Six years' hospital pharmacy experience. Prefers teaching hospital. Registered in Mass. and Conn. Desires to locate in East PW-192

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. Previous hospital pharmacy supervisory experience. Registered in N. Y. prefers to locate in New York City or vicinity. PW-191

STAFF PHARMACIST—Male, married. B. S. One year's hospital pharmacy experience. Registered in N. Y. and Fla. Prefers to locate in Fla. PW-190

CHIEF PHARMACIST—Male, single. B. S. Registered in Minn. and N. D. Prefers foreign anywhere. PW-189

PHARMACIST—Male, single. B. S. received in 1956. One year's hospital pharmacy experience. Would prefer Chicago area. Registered in Mich. PW-186

CHIEF PHARMACIST—Male, married. M. S. Hospital experience. Prefers to locate in East. Registered in N. Y., Mich., N. J., and Fla. PW-184

PHARMACIST—Male, married, B. S. Three years' experience in Sudan Interior Mission Hospital. Prefers to locate in South particularly S. C. Registered in S. C. PW-183

STAFF OR ASST. CHIEF PHARMACIST—Female, single. B. S. Three years' hospital experience. Prefers to locate in Midwest. Registered in Mo. PW-181

PHARMACIST—Male, married. B. S. Interested in career in hospital pharmacy. Prefers to locate in East. Registered in N. Y. and Ill. PW-180

CHIEF PHARMACIST—Male, single. B. S. Four years' hospital experience. Interested in manufacturing and administration. Registered in Conn. Prefers Northeast section of country. PW-179

ASST. CHIEF OR CHIEF PHARMACIST—Male. B. S. received in 1954. Desires to locate in Mich., Ohio or Ill. Registered in Mich. PW-177

ASST. CHIEF OR STAFF PHARMACIST—Female, single. B. S. Registered in La. and Ohio. Prefers Ohio and northern part of country. PW-176

CHIEF PHARMACIST—Male, married. B. S. Registered in Mo. and Kansas. Prefers Southeast or Southwest section of country. Desires position with possibility of assuming administrative duties. PW-174

PHARMACIST—Butler University graduate with Ph.C. degree. Registered in Ill., Ky., Ind., and Ore. Prefers to locate in Midwest. PW-173

PHARMACIST—Graduate Philadelphia College of Pharmacy and Science 1959; 22 months' hospital pharmacy experience. Registered in Pa. Desires position in the East. PW-172

STAFF PHARMACIST—Female. 1957 graduate of the University of Buffalo College of Pharmacy. Registered in N. Y. Prefers to locate in the East. PW-171

PHARMACIST—Female. Graduate of the University of Idaho, 1954. Registered in Ill. Hospital experience. Prefers Chicago area. PW-166

CHIEF OR ASST. CHIEF PHARMACIST—Female, B. S. and M. S. Purdue University. Ten years' hospital pharmacy experience. Registered in Ind. and Ky. PW-164

PHARMACIST—Male. Registered in La. and Mo. Experienced. Prefers Midwest. PW-161

STAFF PHARMACIST—Male, married. Registered in N. Y. and N. J. Prefers New England. PW-157

ASST. CHIEF PHARMACIST—Male, single. Registered in N. Y. and Vt. Served hospital pharmacy internship, now employed part-time staff pharmacist. Prefers Eastern part of country. Has M. S., 4 years' hospital pharmacy experience. PW-154

CHIEF PHARMACIST—Male, married. B. S. Ten years' hospital pharmacy experience. Registered in Mass., Ill., Mo., Ky., Tenn., and Va. PW-150

PHARMACIST—Male, single. B. S. pharmacy, June 1959. Locate East. PW-149

ASST. CHIEF OR CHIEF PHARMACIST—Single, male. Registered in D. C., Ill., Md., and Pa. Graduate University of Pittsburgh in 1953, experience in research. Prefers North and East. PW-148

CHIEF PHARMACIST—Registered in Mo. and Ill. Ph.G. degree. Eight years' hospital pharmacy experience. PW-147

STAFF PHARMACIST—Male, single. Completed military requirements. Hospital pharmacy experience. Prefers East. PW-146

CHIEF PHARMACIST—Prefers N. Y. or N. J. area. Over 20 years' experience as chief pharmacist and purchasing agent. Graduate St. John's College of Pharmacy. Registered in N. Y. and N. J. PW-144

CHIEF PHARMACIST—Male, married. B. S. Conn. registration. Five years' hospital pharmacy experience. Prefers Northeast section of country. PW-140

PHARMACIST—Male, single. Registered in Conn. and N. J. Five years' hospital pharmacy experience. B. S. Prefers Conn. or Texas. PW-123

ASST. DIRECTOR OR DIRECTOR OF PHARMACY SERVICES—Male, single. B. S. Retail and five years' hospital experience. Registered in Ill. PW-119

CHIEF PHARMACIST—Female, single. Registered in Pa. and Ohio. Twelve years' experience as chief pharmacist. Desires to locate in Pa. or Ohio. PW-111

NEW MEMBERS

The following ASHP members sponsored the New Members listed in this issue of the JOURNAL. *The officers of the* SOCIETY *and the Committee on Membership and Organization appreciate the efforts of the individuals who have encouraged New Members to join the national organizations.*

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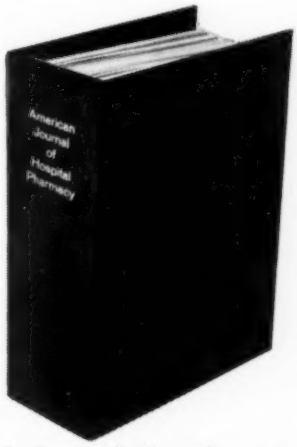
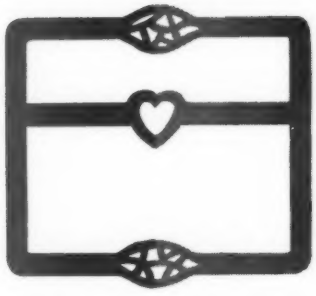


A loose-leaf binder for the AMERICAN JOURNAL OF HOSPITAL PHARMACY is now available from The Hamilton Press, Hamilton, Illinois. The new binder has been designed for THE JOURNAL and will hold the twelve issues satisfactorily. The binder is brown in color and "American Journal of Hospital Pharmacy" is embossed on it in gold. The binder is 9 by 12¼ inches with the spine measuring 4 inches.

The cost of the binder is four dollars ($4.00) each and orders may be directed to The Hamilton Press, Hamilton, Illinois.

ADVERTISERS

January, 1960



FOR GREATER LATITUDE IN SOLVING THE PROBLEM HYPERTENSION WITHOUT SIGNIFICANT POTASSIUM DEPLETION

NEW RAUTRAX

RAUTRAX, a combination of Raudixin with Ademol (flumethiazide)—**the new, safe nonmercurial diuretic**—controls all degrees of hypertension. Elimination of excess extracellular sodium and water is rapid and safe.[1-5] Potassium loss is less than with other nonmercurial diuretics;[1-3] and, in addition, Rautrax increases protection against potassium and chloride depletion during long-term management by including supplemental potassium chloride.

The dependable diuretic action of Ademol rapidly controls the clinical and subclinical edema often associated with cardiovascular disease. And after Rautrax has normalized the fluid balance, the normal serum electrolyte pattern is not altered appreciably by continued administration.[4] Ademol also potentiates the antihypertensive action of Raudixin.[1] In this way a lower dose of each component controls hypertension effectively and safely . . . with fewer side effects.

REFERENCES: 1. Montero, A. C.; Rochelle, J B., III, and Ford, R. V.: New England J. Med 260:872 (April 23) 1959. 2. Fuchs, M.; Bodi, T., and Moyer, J. H.: Am. J. Cardiol. 3:676 (May) 1959. 3. Fuchs, M., and others: Monographs on Therapy 4:43 (April) 1959. 4. Montero, A. C.; Rochelle, J. B., III, and Ford, R. V.: Am. Heart J 57:484 (April) 1959. 5. Rochelle, J. B., III; Montero, A. C., and Ford, R. V.: Antibiotic Med. & Clin. Ther. 6:267 (May) 1959. LITERATURE AVAILABLE ON REQUEST

SQUIBB

Squibb Quality—
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not sweet, not bitter

TESSALON®

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The problem of taste, which can be a hindrance to effective cough therapy, simply does not exist with Tessalon perles. There is no gagging, no refusal, no delaying, no "cheating"—because Tessalon perles provide medication enclosed in *tasteless* gelatin spheres.

Tessalon, a nonnarcotic, is 2½ times as effective as codeine.* Tessalon acts both at the sensory receptors in the chest *and* the cough centers of the medulla. Furthermore, it controls cough frequency without interfering with productivity or expectoration; sputum is usually thinner, easier to raise. Tessalon acts within 15 or 20 minutes, controls cough for 3 to 8 hours. There are no major side effects. Whether for acute or chronic cough, whether for short- or long-term therapy, Tessalon has a remarkable margin of safety. Perles insure built-in, precise dosage—no sugar or sodium to interfere with diet, no problem of nausea. Tessalon perles are easy to swallow, easy to carry in pocket or purse.

SUPPLIED: Tessalon *Perles*, 100 mg. (yellow); bottles of 100. Tessalon *Pediatric Perles* (for children under 10), 50 mg. (red); bottles of 100. *Also available* (for use when oral administration of Tessalon is precluded): *Ampuls*, 1 ml. (5 mg.); cartons of 5.

* Shane, S. J., Krzyski, T. K., and Copp, S. E.: Canad. M.A.J. 77:600 (Sept. 15) 1957.

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SUMMIT, N. J.